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ELECTROLYTE CHANGES IN NEPHROSIS. By CHARLES L. FOX, JR., M.D. and DONOVAN J. McCUNE, M.D. . . . 1

VASCULAR OCCLUSION AND ISCHEMIC INFARCTION IN SICKLE CELL DISEASE. By PAUL KIMMELSTIEL, M.D. . . . 11

AN EVALUATION OF THENYLENE HYDROCHLORIDE N, N-DIMETHYL-N'-(ALPHA-PYRIDYL)-N'-(ALPHA-THENYL) ETHYLENEDIAMINE HYDROCHLORIDE. By ROBERT KIERLAND, M.D. and ROBERT T. POTTER, M.D. . . . 20

ECCHYMOSIS OF THE ABDOMINAL WALL AS AN EARLY DIAGNOSTIC SIGN OF DISSECTING ANEURYSM OF THE AORTA. By RAYMOND GREEN, M.D., F.A.C.S. and OTTO SAPHIR, M.D. . . . 24

THE CLINICAL USE OF A TRIPLE SULFONAMIDE MIXTURE. By JOHN H. LEDBETTER, M.D. and GEORGE E. CRONHEIM, Ph.D. . . . 27

CHOLESTEROL METABOLISM: BLOOD SERUM CHOLESTEROL AND ESTER LEVELS IN 200 CASES OF ACUTE CORONARY THROMBOSIS. By LESTER M. MORRISON, M.D., LILLIAN HALL, M.D. and ALBERT L. CHANEY, Ph.D. . . . 32

PHEOCHROMOCYTOMA OF THE ADRENAL MEDULLA. A CLINICOPATHOLOGICAL STUDY OF FIVE CASES. By S. D. SPATT, M.D. and D. M. GRAYZEL, Ph.D., M.D. . . . 39

AMYLOIDOSIS IN RHEUMATOID ARTHRITIS. A REPORT OF TEN CASES. By PAUL N. UNGER, M.D., MORRIS ZUCKERBROD, M.D., GUSTAV J. BECK, M.D. and J. MURRAY STEELE, M.D. . . . 51

ELECTROENCEPHALOGRAPHIC RECORDS IN RELATION TO BLOOD PRESSURE CHANGES IN ECLAMPSIA. By HUDSON JOST, Ph.D. . . . 57

ADMINISTRATION OF MASSIVE DOSES OF VITAMIN P HESPERIDIN METHYL CHALCONE. By W. R. KIRTLEY, M.D. and FRANKLIN B. PECK, M.D. . . . 64

A SURVEY OF THE TREATMENT OF PERNICIOUS ANEMIA IN RELAPSE: (A) A COMPARISON OF THE HEMATOPOIETIC RESPONSE TO LIVER EXTRACT AND FOLIC ACID (L-CASEI FACTOR). (B) LIMITATIONS OF THE RETICULOCYTE RESPONSE AS A MEASURE OF ANTI-PERNICIOUS ANEMIA POTENCY. By GUY W. CLARK, Ph.D. . . . 71

SEVERE PAROXYSMAL CARDIAC PAIN AS A PRODROME IN IDIOPATHIC EPILEPSY. By J. W. FISCHER, M.D. . . . 78

PROGRESS OF MEDICAL SCIENCE:

MEDICINE. By MAXIMILIAN FABRYKANT, M.D. and MAURICE BRUGER, M.D. . . . 84

NEUROLOGY AND PSYCHIATRY. By CLYDE E. STANFIELD, M.D. . . . 97

PROCEEDINGS OF THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA . . . 114

Contents continued on adv. page 10

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Female	75.8	77.1	78.0	78.6	79.9	81.9	83.9	85.4	86.8	86.8	84.4

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*Blood Pressure. Report of Joint Committee on Mortality of The Association of Life Insurance Medical Directors and The Actuarial Society of America. New York, 1925. pp. 10, 52.

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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

JULY, 1948

ORIGINAL ARTICLES

ELECTROLYTE CHANGES IN NEPHROSIS

Occurrence of Diuresis Following Administration of Sodium And Potassium Salts*

By Charles L. Fox, Jr., M.D.
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The child with nephrotic edema has an excessive volume of extracellular fluid. The chemical composition of his plasma, a small fraction of the total extracellular fluid, is abnormal in that its albumin concentration is markedly reduced. It is a less familiar fact that the chemical composition of the entire extracellular fluid is also abnormal. Thus the concentrations of both sodium and bicarbonate are reduced and that of chloride is increased. The cause of these abnormal concentrations is unknown at present but it is pertinent to ask what effects they might produce.

The decrease in plasma albumin is generally assumed to permit increased amounts of an ultrafiltrate of plasma to pass from the vascular bed into the tissue spaces. Thus hypoproteinemia is commonly thought to be responsible for the edema. However, it has been observed repeatedly that loss of edema can occur without elevation of plasma protein, which may remain pathologically low for weeks or months after edema has been lost through diuresis. In contrast, the reduction in plasma sodium makes it possible for water to migrate from the extracellular compartment into the cells of the body, causing intracellular edema. The lowered plasma bicarbonate and elevated chloride are characteristic of chronic acidosis which also produces a shift of water into tissue cells.[11,22,29]

Shifts of extracellular water have important secondary effects. Thus transfer of extracellular water into cells (as in the Darrow-Yannet experiment[6,13] or after sodium depletion in man[17]) reduces the plasma volume. Reduction of plasma volume by sodium depletion[13] has been shown to result in decreased glomerular filtration and delayed excretion of water.[12,17] Although

* This paper was read at a meeting of the Society for Pediatric Research at Stockbridge, Massachusetts, on May 12, 1947.
† Aided in part by a grant from the U. S. Public Health Service.

renal function studies in nephrosis have resulted in both super and subnormal clearances,[7] the studies of Oliver[20] indicate the need for considerable caution in interpreting such measurements. Certainly the clearance of water and sodium is not increased. The effects of intracellular edema on the function of organs, such as the kidney, can only be surmised at present. In any event, reduced plasma volume might interfere with nutrition of cells; this added to the chronic acidosis and intracellular edema, would presumably augment the loss of potassium from body cells. These may also have suffered intrinsic damage from the disease itself.

Table 1.—Typical Plasma and Urine Electrolyte Concentrations in Nephrosis
(All concentrations are expressed in mEq. per liter)

	Na	HCO_3	Cl	K	HPO_4	H
Plasma	132	14	108	5	2	0 0001
Urine	10	0 01	10	180	70	0 01
U/P ratio	0 1	0 001	0 1	36	35	100
Normal Values						
Plasma	142	27	103	5	2	0 0001
Urine	140	10	100	50	20	0 001
U/P ratio	1	0 3	1	10	10	10

If these suppositions are true, the composition of the urine should reflect these disturbances. The urine would be scanty in volume, acidic in reaction, and low in sodium but high in potassium. These inferences are consistently fulfilled while edema persists, thereby attesting the kidneys' ability to protect homeostasis as far as possible in this difficult situation. Average values found in all children we have observed, together with normal values, are summarized in Table 1. Similar plasma values have previously been noted[1,2,4,11] but not correlated with the edema and oliguria.

In view of these chemical abnormalities, it seemed reasonable to anticipate that administration of sodium bicarbonate (in the form of its precursors, i. e., lactate or the more rapidly convertible acetate) might produce two important results: (1) elevate the concentration of sodium in extracellular fluid and the concentration of bicarbonate in both extracellular and intracellular fluids; (2) move water out of cells thereby further expanding both plasma and extracellular volumes. Certain changes in kidney function would then follow: the *filtration of sodium* would increase markedly. Furthermore, as shown by Pitts,[25] when the excretion of bicarbonate at high plasma levels is greatly increased in association with accelerated urine flow, chloride reabsorption is decreased and chloride is excreted in the urine. Apparently the capacity of the tubules to reabsorb chloride can be reduced by presenting to them simultaneously an excess of bicarbonate. Excretion of chloride is desired as a means of removing extracellular fluid.

The administration of potassium would presumably permit its replacement in cells as the total osmotic pressure (not that of the colloids alone) of extracellular fluid was increased by sodium administration. In view of the osmotic equilibrium between the potassium concentration inside the cells and the sodium concentration of the surrounding medium,[11,22] the intracellular concentration of potassium cannot be raised to normal until the extracellular concentration of sodium is likewise raised to normal. Thus administra-

tion of potassium only has not proven effective although excess potassium promotes water excretion.[30] Excess bicarbonate formed from potassium acetate would further augment bicarbonate excretion and thereby add to the strain on the chloride reabsorptive mechanism.

Finally, the introduction of considerable alkaline electrolyte into the tubular urine might inhibit precipitation of protein in the renal tubules, as suggested by the *in vitro* experiments of Oliver.[19]

Methods: Sodium and potassium in plasma and urine were determined by the lithium internal standard flame photometer,[3] the use of which for biological fluids has been described.[9] In R. W., plasma sodium was determined by a gravimetric uranyl zinc acetate method after dry ashing. Chlorides were determined by the method of Schales and Schales;[27] alkaline urines were brought to the correct pH for titration by one or two drops of 3 per cent nitric acid. The other analyses were performed by the hospital laboratories using standard methods.

Procedure and Observations: Observations have been made in children with massive edema and ascites, hypoproteinemia (A/G ratio less than one) and marked proteinuria but without hyperazotemia. The urine contained small numbers of red cells and occasional granular casts; hypertension was absent or minimal; lipemia was marked. The presumptive diagnosis in these children

TABLE 2.—SUMMARY OF BALANCES OF SODIUM, CHLORIDE AND POTASSIUM
(All data are for 30 day periods of observation)

Patient	Age	Body weight (kg.) Initial	Final	Loss	Na	Cl	K
					(Total milliequivalents in 30 days)		
Diuresis Following Administration of Sodium Lactate (1 Molar Solution)							
R. W.	7	43.9	25	18.9			
Recovered in urine (42.4 l.)					−9080	−3943	−1153
Recovered in 4.8 l. ascitic + 0.7 l. pleural fluid					− 800	− 605	− 28
Intake of sodium lactate					+6750		
Diet (estimated) + penicillin infusion—1.8 l.					+1170	+1170	+ 900
Balance					−1960	−3378	− 281
Weight loss × concentration in E.C.F.					+2640	+1980	+ 95
Net					+ 680*	−1398*	−186
Spontaneous Diuresis							
G. B.	8½	46.3	31.7	14.6			
Recovered in urine					−5400	−5500	−1250
Diet (estimated)§§					+1200	+1200	+1200
Balance					−4200	−4300	− 50
Weight loss × concentration in E.C.F.					+2050	+1530	+ 75
Net					−2150	−2770†	+ 25
Diuresis Following Administration of Sodium and Potassium Acetate							
R. P.	3½	24	18	6			
Recovered in urine					−7300	−2455	−3600
Medicinal intake					+8000‡		+4000
Diet (estimated)§§					+ 900	+ 900	+ 900
Balance					+1600	−1555	+1300
Weight loss × concentration in E.C.F.					+ 840	+ 660	+ 30
Net					+2440‡	− 895	+1330

* Sodium and chloride continued to be excreted in the urine in considerable quantity above their intake for remaining 8 days of hospitalization. Inclusion of these amounts would balance the sodium column and increase the excess chloride excretion.

† Although this total may seem excessive, the urine chloride concentration frequently ranged from 200 to 254 mEq. per liter during chloruresis; (See Fig. 2).

‡ These values may be too high because some sodium was lost by vomiting and error in sodium dosage initially. There was also considerable excess sodium excretion in the week following this 30-day collection period; some lag in sodium excretion follows administration of large amounts.

§§ Diet low in Na. and Cl. only partially consumed because of anorexia and emphasis on Na. and K medication intake.

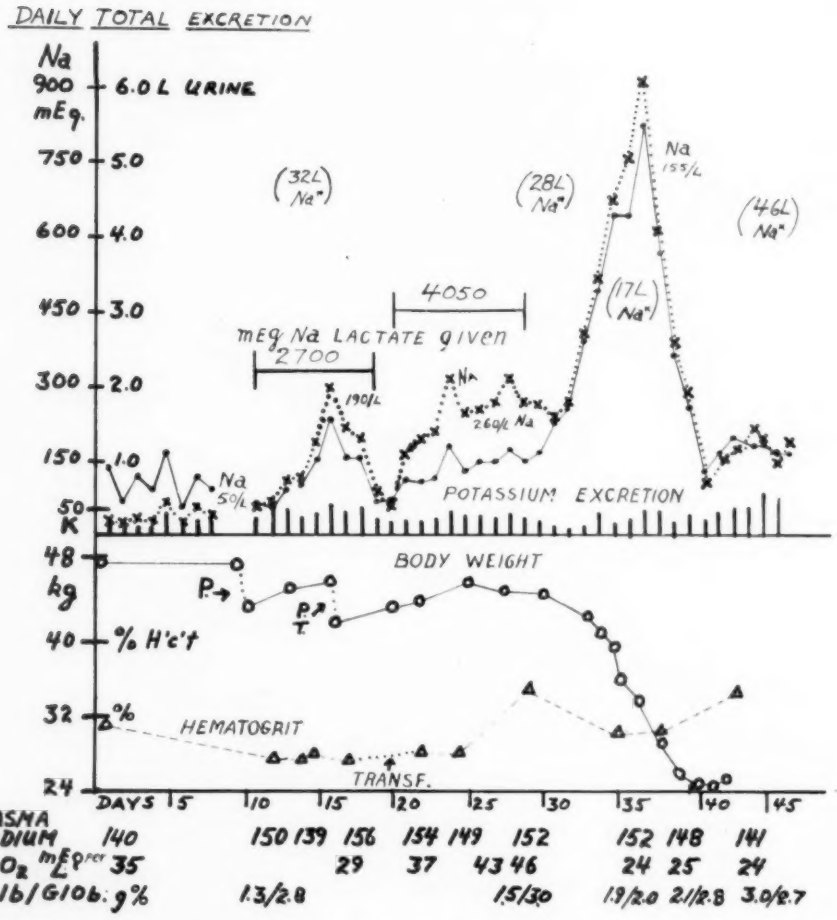

FIG. 1.—Changes after giving sodium lactate, 1 molar 400 cc. daily, and the effect of sodium lactate administration on nephrosis with massive anasarca. (RW 7 years.) The volume of urine (solid line) and its content of sodium (dotted line with crosses) are plotted on the vertical axis with the scales adjusted so that 1000 cc. of urine corresponds with 150 mEq. of sodium. This facilitates recognition of changes in urine composition, *e. g.*, when the sodium concentration in the urine is 150 mEq. per liter, the points for urine volume and total sodium coincide; when the concentration of sodium in the urine is greater than 150 mEq. per liter, the point for total sodium falls above the point for volume and *vice versa* for dilute urine. Representative values are printed on the chart. The amount of sodium lactate administered in the interval between the vertical lines is printed over a horizontal line placed at a level on the sodium scale which corresponds to the average daily sodium intake. The values in parenthesis are the liters of sodium space (12) represented by the apparent volume of distribution of radiosodium 15 hours after injection.

The daily potassium excretion is shown by the height of the vertical lines; 50 mEq. of K is marked on the ordinate. Body weight is plotted below; at the vertical arrows and capital P, 7 and 4.8 liters of ascitic fluid and 0.7 liter of pleural fluid were moved. The hematocrit values are plotted to indicate relative changes in blood volume.

At the bottom of the chart are plasma values of sodium and bicarbonate in mEq. per liter and for albumin and globulin in grams per 100 cc. of plasma; the A/G ratios were below unity.

During the first 10 days of observation, small volumes of acid urine low in Na were obtained. Sodium lactate was then given cautiously; plasma Na increased and the concentration of Na in the urine rose rapidly to 210 mEq. per liter (day 15); urine volume tripled. Then the plasma Na decreased (day 13) suggesting a movement of water from cells into extracellular fluid. Continuation of sodium administration and excretion of more water than sodium in the urine raised plasma Na to 156 mEq. per liter (day 17). When sodium administration was interrupted, both the volume of urine and its concentration of Na decreased promptly. With further sodium administration, the volume of urine rose only slightly but the concentration of Na increased sharply to 274 mEq. per liter (day 27). Although lactate was not given after the 29th day, the plasma Na remained over 150 mEq. per liter; urine Na decreased to this level and the urine chloride increased from 15 to 25 mEq. per liter to equal and then exceed (142 mEq. per liter) the plasma chloride as the daily volume of urine rose to a maximum of 5.5 liters on the 36th day.

The change in the appearance and behavior of the child was dramatic as the massive edema and anasarca rapidly disappeared and the body weight was halved. Just prior to diuresis, the potassium concentration of the urine dropped sharply to 7.7 mEq. per liter (day 31) and remained in this range for 10 days. In the subsequent days, electrolyte values in plasma and urine became normal. The protein content of the urine fluctuated from 1.9 to 4.3 gm. per day. No additional therapy was given and the child was discharged edema-free. It was of further interest that the hematocrit of 31% decreased to 27% with sodium administration and then rose to 35% after diuresis. The proteins decreased from 4.1 to 3.88 gm. per 100 cc. prior to diuresis. These values suggest expansion of plasma and extracellular volumes prior to diuresis with subsequent decrease toward normal.

was either lipoid nephrosis or the nephrotic phase of glomerulonephritis.

The first child studied had remained edematous for 15 weeks. He received sodium lactate as a one molar (six times isotonic) solution by mouth. Fluids were moderately restricted but not to the point of marked thirst. The sequence of events, summarized in Figure 1, was as follows: The volume of urine and the concentration of urinary sodium increased. The plasma sodium rose, then fell, apparently as a result of movement of water from cells to the extracellular compartment. With additional intake of sodium, plasma sodium increased to over 150 mEq per liter and remained elevated. The plasma bicarbonate increased slowly; in contrast, urine bicarbonate increased rapidly, values above 300 mEq. per liter having been observed.

The apparent extracellular volume, (Na^*) in Figure 1, as measured by radiosodium[15] decreased slightly, as did body weight.

After seven days, with urine sodium and bicarbonate in excess of 250 mEq. per liter, chloride reabsorption apparently failed; urine chloride suddenly rose from under 15 mEq. per liter to that of the plasma and above. Urine sodium decreased from 270 mEq. per liter to 155, equalling plasma concentration. Thus the urine being excreted required minimal osmotic work on the part of the kidney.[18] At this point, four days after the last dose of sodium lactate, the volume of urine increased by a liter per day to reach 5.5 liters daily and the sodium and chloride concentrations remained approximately equiosmotic with the plasma.

During this period edema and ascites disappeared; body weight and extracellular volume returned to normal. Plasma proteins remained virtually unchanged during the 40-day period except for a decrease from 4.5 to 3.9 gm. per 100 cc. at the peak of diuresis.

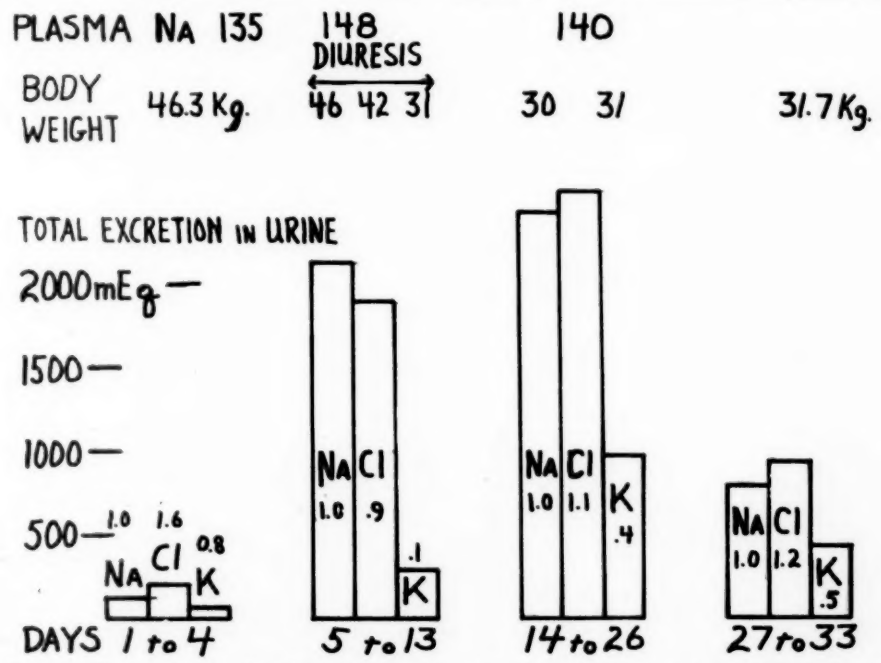

FIG. 2.—Electrolyte excretion in spontaneous diuresis. Urine Na increases to equi-osmoticity with the plasma as plasma Na increased from 135 to 148 mEq. per liter and urine volume increased 5-fold. Chloride excretion rose sharply; body weight decreased. After the 12th day no further decrease in body weight occurred; nevertheless, excretion of Na, Cl and K continued at high levels for over 2 weeks. The average mEq. excreted per diem of Na, Cl and K respectively in each period are days 1 to4: —29, 48, 23. Days 5 to 13:—236, 211, 31. Days 14 to 26:—186, 196, 67. Days 27 to 33:—109, 131, 59. The ratios of the excretion of Cl and K to Na taken as 1.0 are placed above the symbols in each box.

The total amount of sodium excreted represents the sum of the sodium administered plus the amount derived from the volume of edema fluid removed. In contrast, the overall balance sheet in this child, and also in all others similarly studied (Table 2), brings to light an enormous store of chloride

which was jettisoned in excess of that expected from the volume of edema fluid. The site of the excess chloride is not known; the cells are suspected and, indeed, the erythrocytes of all children measured showed increased chlorides ranging up to twice the normal value. The shift of chloride into red cells has been studied by Van Slyke[29] and Peters[23] and is rather characteristic of acidosis, the presence of which was inferred at the outset from the persistently lowered plasma bicarbonate. (See Figure 4). The exact degree of acidosis needs to be established by measurement of pH. Furthermore, the excess chloride is only partialy accounted for by increased concentrations in the red cells. Obviously, analyses of other tissues is required to settle this point.

The frequent occurrence of spontaneous diuresis in this syndrome provided an opportunity to study such an episode in another patient. The total electrolyte excretion and the ratio of potassium and chloride to sodium in the urine, together with the changes in body weight, are shown in Figure 2. During the period of maximal edema there was a relatively high potassium excretion. This has been a consistent finding. It strongly indicates intracellular derangement and suggests the need for potassium administration. It is also worthy of note that the chloride

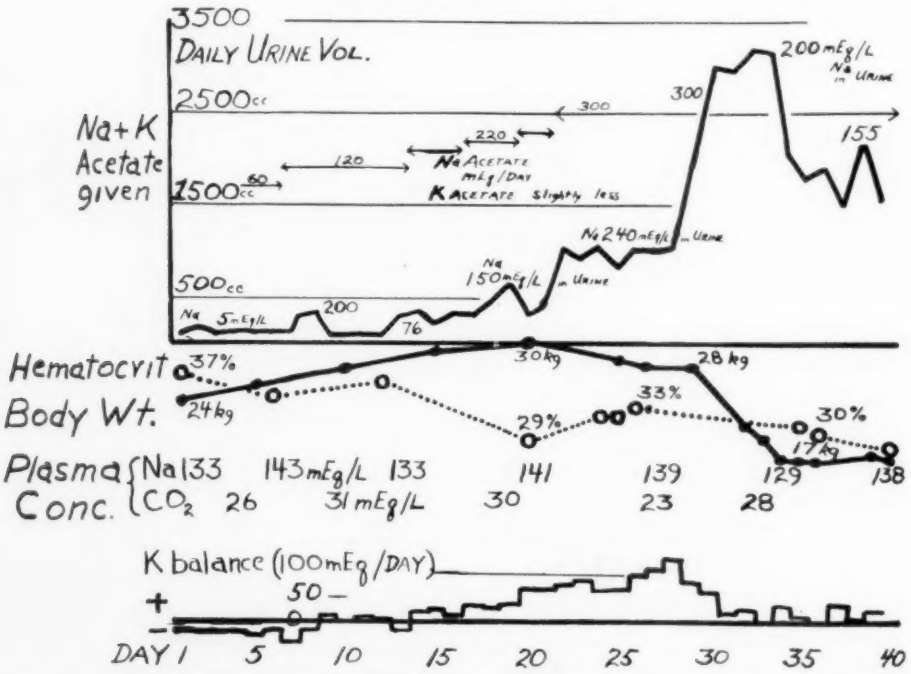

FIG. 3.—Changes after sodium and potassium acetate *per os*. The upper solid line shows daily urine volume and its average concentration of sodium is printed along the curve. The inverse relationship of body weight and hematocrit are indicated below. It would appear that blood volume increased with Na and K administration prior to diuresis. Plasma sodium was increased with a moderate increase in plasma bicarbonate. Diuresis in this instance occurred with hypertonic urine and consequently plasma sodium was carried below normal, then returned to normal. The potassium balance (not including diet) is indicated; retention of 980 mEq. occurred from the 17th to 30th day inclusive. This is considerably in excess of a reasonable allowance for potassium in the food consumed during this 2 week period of anorexia associated with the large intake of not especially palatable medication.

excretion considerably exceeded the sodium output. After having been edematous for nine weeks, during a few days of observation in this hospital without any attempt at treatment a minor crysipeloid infection occurred, plasma sodium rose from 135 to 148 mEq. per liter and the urine composition suddenly approached that of extracellular fluid. For the next few days the U/P ratio of sodium and chloride approached unity and urine of a concentration representing minimal renal osmotic work[18] was excreted in increasing volume as ascites and edema disappeared and body weight decreased to normal. Then followed a period of strikingly greater sodium and chloride excretion *but no weight loss.* Inasmuch as potassium excretion increased sharply at this time, it would appear that the normally extracellular sodium and chloride, together with potassium, left the intracellular compartment. The overall balance sheet (Table 2) shows a rather large excess excretion of chloride, similar to that mentioned above, after the induced diuresis. In relation to the weight of edema and ascitic fluid lost, the sodium excretion was twice that expected; the chloride excretion, however, was three times that expected. There was also considerable potassium excretion at certain intervals. These shifts of electrolytes without water focused our attention on the intracellular compartment, the site of enzyme activities, in searching for an explanation of this syndrome. In any event, increase of intracellular pH from below normal, by elevation of the pH of extracellular fluid and shift of additional bicarbonate into cells with restoration of Donnan's equilibrium between cells and extracellular fluid, could account for this removal of electrolytes (chiefly chloride) from cells. In this connection, the experiments of Rapoport and Guest[26] and Peters[23] have indicated the type of changes that might occur in cells with changes of their pH.

During the past six months, the interest of Dr. Murray Bass and the cooperation of Dr. Jerome Kohn and Dr. Ralph Moloshok at Mt. Sinai Hospital have afforded additional opportunities of profiting by earlier experience.

The schedule of dosages carried out by Dr. Moloshok and the measurements made in our laboratory are shown in Figure 3, which contains observations on a third patient. This child had been edematous for nine weeks and there was an additional period of observation for basal values. Then sodium acetate therapy was begun but potassium administration deferred (although plasma potassium was below normal) because the urine volume was scanty. Plasma and urine sodium both rose, urine volume increased and there was a gain in weight of 5 kg. in 16 days. Sodium and potassium acetate were pushed; whereupon the hematocrit decreased, suggesting an increase in plasma volume; the urine sodium and bicarbonate fell toward normal; retention of potassium occurred; urine chloride rose from 15 mEq. per liter to the level of plasma chloride. With urine electrolytes nearly equiosmotic with the plasma, the volume of urine rose sharply and body weight decreaesd as ascites and edema disappeared. The balance sheet here (Table 2) is more complicated, but again the chloride excreted greatly exceeded the amount anticipated from the volume of edema lost. Although dietary intake was not measured precisely, there seems to have been potassium retention.

The question of alkalosis always arises. Figure 4, from Gamble's monograph,[11] helps explain why it has not caused tetany, except in one patient classified as chronic nephritis; doubling plasma bicarbonate requires only a small increase of carbonic acid to prevent an undesirable rise in plasma pH. When the medication is increased gradually, urinary excretion of bicarbonate rises to over 300 mEq. per liter and its output almost parallels intake. Large amounts of sodium bicarbonate and sodium lactate have been administered to patients with acidosis associated with extensive thermal burns,[8] with renal obstruction from sulfona-

mides,[14] and to prevent renal obstruction during massive sulfadiazine therapy.[10] Alkalosis did not occur in these instances and urinary output increased markedly.

Discussion: It is important to emphasize that this study is presented as an experimental approach to the problem of nephrotic edema. More cases are needed to distinguish between therapeutic effect and spontaneous diuresis. To date, diuresis has occurred in 14 children after administration of these salts sufficient to raise plasma sodium to 140 mEq. per liter or over and urine sodium to 200 mEq. per liter or over; a detailed report will be published shortly. In the presence of marked signs of renal damage, changes in plasma sodium and bicarbonate con-

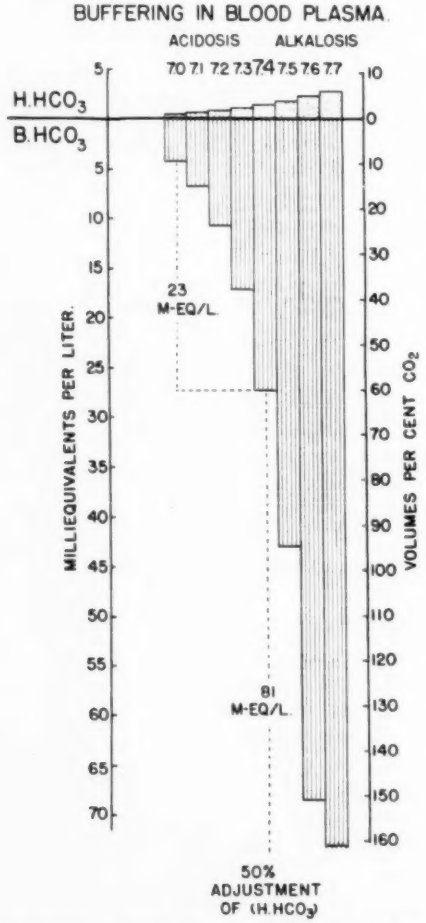

FIG. 4.—Buffering in blood plasma. (From Gamble.) Plasma pH is adjusted by the ratio of H_2CO_3 (above the zero line) to $BHCO_3$ (below the zero line). The normal ratio is 3/60. Consequently, relatively huge increases in $BHCO_3$ cause but slight change in pH when a small and easily accomplished increase in H_2CO_3 follows. In this diagram 50% adjustment by H_2CO_3 is shown; only small increases in pH occur with very large increases in $BHCO_3$.

It is doubtful if plasma pH exceeded 7.5 since plasma CO_2 values in excess of 95 volumes % were seen only once and that child showed no manifestations of alkalosis with a CO_2 of 120 volumes %.

Nevertheless, tetany occurred in 2 patients with poor renal function and should be watched for and guarded against. Inhalation of 10% CO_2 and 90% oxygen gave prompt relief.

centration may occur more rapidly, hence dehydration and tetany need to be guarded against by frequent plasma analyses.

More time is needed to evaluate the effects of sustained electrolyte administration on the signs of renal damage: hypertension, azotemia, casts, red and white cells as well as the massive proteinuria. One three-year-old child has been observed for 28 months, subsequent to diuresis following administration of sodium lactate. During this period sodium and potassium medication has been continued and up to the time of writing the child has remained clinically well, free of edema and without protein or abnormal urinary sediment. Other children receiving medication 6 to 8 months after diuresis have remained edema-free but without subsidence of proteinuria. (The intake of sodium and potassium acetate is adjusted to obtain approximately 140 mEq. per liter of Na and 100 mEq. per liter of K in the pooled 24-hour urine. From 5 to 15 grams of each salt per day have been required.) In our very meagre experience, children kept on maintenance therapy have remained free of edema longer than those not so maintained. Obviously, study of many patients for a period of years is necessary for final evaluation. Preliminary studies by Osman[21] and Schultz[28] did not indicate any increase in life expectancy with somewhat similar management but the factors of renal osmotic work,[18] inhibition of protein precipitation in the tubular urine,[19] chronic acidosis, reduced plasma sodium concentration and potassium replacement have not been studied heretofore.

The great excess of chloride recovered in the urine after diuresis needs careful study. It appears to be greater in those children who subsequently have the longest remissions. Complete metabolic balance studies are essential; in their absence, calculated intakes together with urine chlorides 1.5 to 2.0 times the plasma concentration indicate excess excretion. A dry storage of chloride has been suggested previously[5] and some lipoid-chloride has been described.[24] Furthermore, the *in vivo* experiments of Wilde[30] demonstrate the presence of chloride in *muscle fibers* and also delineate a shift of chloride and potassium into muscle fibers as the sodium content of the extracellular fluid is lowered and its potassium increased. Complete potassium balances are also essential to establish the retention indicated by the present data.

Summary. Significant abnormalities in the concentration of electrolytes in plasma and urine in children with nephrotic edema are described. Diuresis occurred following administration of sodium lactate and sodium and potassium acetate. The electrolyte changes during these episodes and in the course of spontaneous diuresis are presented.

We are indebted to Miss Betty B. Freeman for her painstaking care in performing the electrolyte analyses and for her patience in carrying out numerous comparative gravimetric analyses to establish the accuracy of the lithium internal standard flame photometer.[3,9]

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VASCULAR OCCLUSION AND ISCHEMIC INFARCTION IN SICKLE CELL DISEASE*

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From the accumulated reports of clinical and postmortem observations of cases of sickle cell disease the following concept of its pathology has been formed. The abnormal shape of the sickled erythrocyte is responsible for the stasis of blood flow in capillaries, resulting in thrombosis and subsequent infarction. The principles of this concept, with added modifications, have been accepted by most writers.

We had the opportunity to observe a case of uncomplicated sickle cell disease which revealed multiple foci of ischemic necrosis of inner organs without thrombotic occlusion of arteries. In view of the seeming rarity of such a finding, we believe it to be justified to put this case on record. Also from a review of the literature we have gained the impression that interpretations from repeated and transmitted quotations have outgrown the reported facts. We have attempted, therefore, an analysis of previous reports with particular reference to vascular occlusions in sickle cell disease and its relation to ischemic infarction.

Summary of Case History. Pleasant S., an 11 year old colored female, was admitted to the Poliomyelitis Unit of the Charlotte Memorial Hospital because of weakness and hypo-esthesia of the extremities which had steadily been increasing for the preceding 4 weeks. She complained of moderate abdominal distress.

The left extremities were more affected than those of the right. The child stated that she had recurrent episodes of right upper abdominal distress of approximately 4 to 7 days duration. These symptoms regressed spontaneously but were followed by a period of extreme weakness. During these periods the mother noted slightly icteric scleræ.

On *admission* the child complained of pain in the left extremities. Temperature was 100° F., pulse 90, respiration 20. She was poorly nourished and appeared lethargic. The left extremities could not be moved voluntarily. There was no icterus at this time. Moderate rigidity was demonstrable in the right epigastric and right hypochondriac regions of the abdomen, with severe tenderness in the right upper quadrant and in the midclavicular line. A mass was definitely palpable at this point, measuring approximately 5 cm. in diameter. It seemed to be attached to the inferior surface of the liver. Direct and rebound tenderness were referred to this area. Peristaltic sounds were markedly diminished in frequency and volume.

Neurologic Examination. The reflexes were slightly hyperactive on the right and definitely hyperactive on the left where pathologic reflexes were elicited with ease. Abdominal reflexes were diminished in all 4 quadrants. There was increased tonicity with diminution of muscular power in the left extremities. Position and vibratory sensations were intact.

Laboratory Examination on Admission. White blood cells, 26,000 per c.mm. (neutrophils, 91%); red blood cells, 3,210,000; hemoglobin (Sahli), 6 gm. (41%). Two days prior to admission there were 15,000 white blood cells per c.mm. and 3,800,000 red blood cells; hemoglobin (Sahli), 52%. Blood Wassermann and Kahn were negative. Examination of spinal fluid (2 days prior to admission) revealed a markedly increased pressure with 10 cells per c.mm. No further information was available. Urine: albumin 1+ with occasional red blood cells and white blood cells, as well as occasional granular casts.

Clinical Course. The temperature gradually increased, as did the abdominal symptoms. The patient was placed upon a penicillin regimen. A flat Roentgen ray plate

* The author is indebted to the Heineman Foundation for the illustrations used in this paper.

of the abdomen revealed numerous calculi in the area of the gall bladder. A tentative diagnosis of acute cholecystitis was made. Laparotomy was performed 1 day after admission. During operation a friable necrotic gall bladder was removed. A blood sample was taken on the day of operation for determination of active or latent sickling and "97% active sickling" was reported 12 hours after operation. The condition of the patient became increasingly poor. Ieteric scleræ were noted 8 hours postoperatively. She expired in hyperpyrexia 48 hours postoperatively.

Autopsy. (1 hour 30 minutes after death.) *Lungs:* There were extensive areas of atelectasis and bronchopneumonia in both lungs. No vascular changes (including thrombosis) were found on gross or microscopic examination. *Spleen:* The spleen was grossly not definitely recognizable. In its place was found an ill-defined area of thickening at the inferior surface of the diaphragm which measured approximately 2 x 2 x 0.5 cm. It was very firm in consistency and appeared to consist of a tough whitish capsule containing small dark red vascular areas. Microscopically, this portion of tissue consisted of extremely thickened, hyalinized trabeculæ containing residual vessels with marked calcification. Hematoidin crystals were closely intermingled with calcium deposit. A few residual sinusoids filled with red blood were encountered. Lymph follicles proper were not identified. *Kidneys:* The entire cortex of both kidneys was mottled by numerous yellowish gray, sharply demarcated foci of rhomboid or wedge-shaped configuration. Many of them were confluent. Most of them did not involve more than the outer 1 cm. of the cortex and were slightly elevated over the surface as well as the cut surface. The cortical architecture of the renal parenchyma within these foci was completely obscured. The dissectable blood-vessels were patent throughout. Microscopically, the above-described areas were typical of ischemic necroses with margins of neutrophil infiltration. Platelet thrombi were found in some glomerular tufts and occasionally in capillaries and arterioles within the infarcted zones but no thrombi and no endothelial proliferation were noted elsewhere. Within the normal portions of the parenchyma the capillaries, particularly those of the glomerular tufts, were markedly engorged with red blood cells. *Gall bladder:* (Surgically removed.) Revealed almost complete necrosis of all layers of its wall without inflammatory reaction. It contained 8 faceted bilirubin cholesterol-calcium stones. No vascular occlusion was demonstrated. *Liver:* The consistency was somewhat friable. Many sharply demarcated areas were noted in the right lobe. They were rhomboid in shape, yellowish in color on the cut surface, with completely obscured architecture. Many of them were surrounded by a narrow hemorrhagic zone. The dissectable vessels were patent throughout. Microscopically, scattered large foci of coagulation necrosis were found, mostly in the center of liver lobules. These were surrounded by zones of neutrophilic infiltration which were followed by zones of marked hyperemia. The liver cells in the better preserved portion were filled with coarsely granular bile pigment. Vascular changes, particularly thromboses, were not noted. *Brain:* The gyri were slightly flattened and the sulci narrowed. Numerous foci of degeneration were found, characterized by depression of white matter, in both hemispheres. These foci were light grayish yellow in color and softer than the normal-appearing white matter in some portions and firmer in others. They were sharply demarcated and irregular in shape and size, the largest measuring 4 cm., involving almost the entire white matter of the left posterior temporal lobe, anterior parietal lobe, and encroaching somewhat upon the internal capsule. Other foci, including the posterior portion of the corpus callosum, were observed. The gray matter appeared mainly involved, as were the basal ganglia. Microscopically, numerous, often closely packed, large foam cells were found within the areas of demyelinization of the white matter. The myelin sheaths had completely disappeared and a network of delicate glial fibers had remained. In most of the larger foci the axon cylinders were also completely disintegrated. In some areas, particularly in the corpus callosum, marked glial scarring in the vicinity of foci of demyelinization could be demonstrated. Occasional accumulations of red cells were encountered in perivascular lymph spaces and some of the sections showed considerable accumulations of small round cells, as well as some foam cells, in the Virchow-Robin lymph spaces. Some

FIG. 1.—*Kidney.* Ischemic infarction with extended area of incomplete ischemic necrosis (*A*) in which some preserved glomeruli can be observed

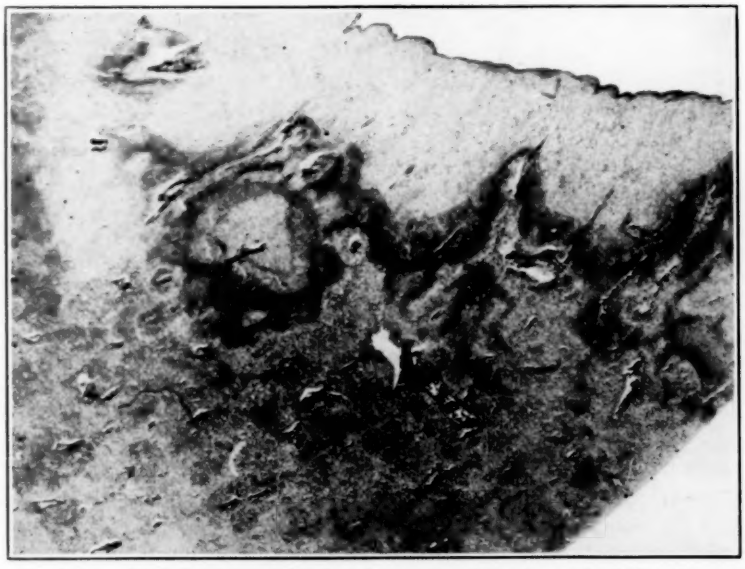

FIG. 2.—*Liver.* Low power magnification shows extensive subscapular ischemic necrosis.

iron pigmented macrophages were also found.

In none of the vessels, small or large, was there found thrombotic occlusion or endothelial proliferation. Fat could not be demonstrated in capillary lumina.

SUMMARY OF CASE. An 11 year old colored girl who was admitted to the hospital with the suspected diagnosis of poliomyelitis went into sickle cell crisis. Because of the clinical picture of "acute surgical abdomen" and the presence of gall stones, the gall bladder was removed. Death occurred 2 days later. The postmortem examination revealed diffuse bi-

FIG. 3. *Cerebral cortex* shows large area of softening in white matter. (Nigrosin Stain, according to R. C. Beck[5])

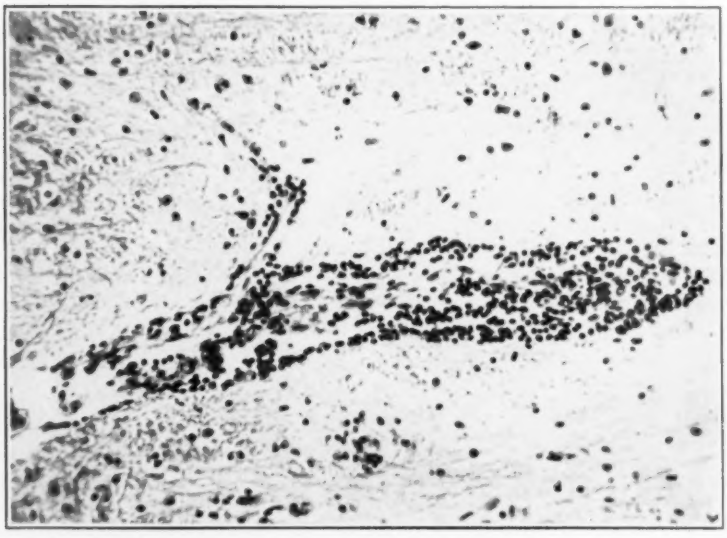

FIG. 4.—*Brain.* Marked perivascular round cell infiltration within areas of ischemic softening.

lateral cortical necroses of the kidney, difuse ischemic infarctions of the liver, ischemic necrosis of gall bladder and multiple large foci of necrosis in the brain. Sickle cells and engorgement of capillaries were prominent but vascular thrombosis was absent. The only condition to which all of the clinical symptoms and pathologic changes could be attributed was the presence of marked sickling of red blood cells and anemia.

Discussion. As indicated in the introduction, we found it difficult to reconcile the morphologic findings in this case with the current consensus, according to which the ischemic infarctions are attributable to capillary blockade followed by arterial thrombosis.

Capillary engorgement has often been described as a prominent finding. Diggs and Ching,[6] in particular, have drawn our attention to this phenomenon and it has

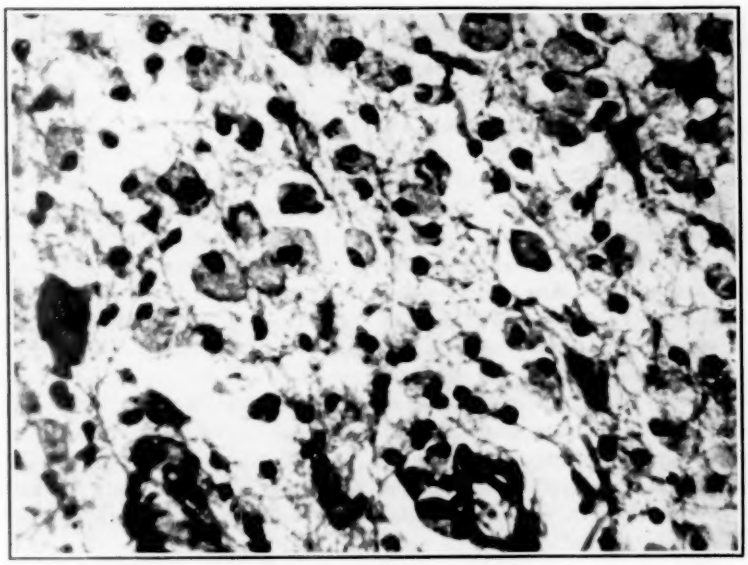

FIG. 5. *Brain.* Accumulation of "foam cells" within area of ischemic softening.

been concluded that the odd-shaped, rigid erythrocytes block the capillaries. This process is supposed to initiate capillary stasis which in turn is followed by thrombosis (Murphy and Shapiro,[14] Bauer[1]). Our case, likewise, shows marked capillary engorgement and areas are encountered where the packing of red blood cells resembles conglutination.

An interpretation of these microscopic observations, in our opinion, must take into consideration the fact that capillary stasis, for the most part, is transitory in nature. Only exceptionally are true capillary thrombi formed. It is hard to reconcile the transitory character of the stasis with a mechanical blocking of the capillaries by sickled cells.

Reëstablishment of capillary flow may conceivably come about by disintetration of red blood cells. Bauer[1] postulates such disintegration resulting from "conglutination." If the reëstablishment of circulation, however, were due to massive disintegration of red blood cells in all of the static capillaries, we would expect evidence of intravascular hemolysis. This has not been demonstrated. It has been pointed out that hemoglobinuria is absent (Haden[10]), and destruction of red blood cells is, therefore, believed to take place in the reticuloendothelial system.

As long as the red blood cells are "packed," they cannot obtain sufficient oxygen to regain their spherical shape and elasticity. It is, therefore, obvious that the rigid sickled cell, unless destroyed, must pass as such through the bottle-neck when the crisis recedes. This can only be explained by widening of the capillary bed or increase of peripheral blood pressure. Hence, it is our opinion that the engorgement of capillaries does not result from purely mechanical block by sickled cells. We assume that functional changes of the peripheral vascular apparatus are the cause of stasis as well as reëstablishment of blood flow.

Arterial thrombosis does not fully account for the ischemic necroses of inner organs. Our own observation appears to be ample proof that other factors than mechanical occlusion may be responsible for this change. Thrombi, particularly in cerebral vessels, undoubtedly occur in cases of uncomplicated sickle cell disease but not as consistently as one is led to believe.

If one disregards the numerous statements of arterial thrombosis merely based on partially correct and partially errone-

ous quotations, the actual occurrence appears to be limited to a relatively small number of cases. In fact, we have only been able to find definite evidence of thrombosis in the cerebral vessels in 4 cases (Hughes, Diggs and Gillespie;[12] Connel;[5] Tomlinson;[18] Bridgers[4]). Frequent reference is also made to thrombi in lungs, spleen and other inner organs.

In checking such references as are available we have not been able to find convincing evidence. Wertham, Mitchell and Angrist[21] reported pulmonary infarctions and thrombosis (Case 1) but do not exclude its embolic origin. In their second case, pulmonary infarctions were found histologically but thrombosis was not mentioned. Mallory[13], reported numerous pulmonary infarctions in a case of sickle cell disease, complicated by sepsis and rheumatic fever. He stressed the fact that thrombi could hardly be found outside the infarcted regions proper. We infer that these thrombi were probably secondary to the tissue necrosis rather than their cause.

Infarcts in the spleen, according to Diggs and Ching,[6] are common but they add that no thrombi in arteries or veins are noted. "Smaller arterioles," however, show endarteritis and thrombosis. These, in our opinion, do not account for grossly noticeable infarctions. Wertham, Mitchell and Angrist,[21] for instance, reported an isolated recent infarct in the spleen with a mural thrombus in an arteriole which was included in the area of infarction. Wade and Stevenson[19] spoke of areas of "pale staining necroses" in the spleen but reported no thrombi. Bridgers[4] (Case 2) described a large splenic infarction without being able to demonstrate thrombi grossly or microscopically. Hein and Thorne[11] spoke of areas in the spleen which were grossly suspected to be infarctions but which upon histologic examination failed to reveal necrosis. On the other hand, Bennett[3] reported thrombosis in small and medium-sized arteries in the spleen but no infarctions.

Infarctions in the liver or, at least, foci of necrosis have been mentioned (Bennett[3]) but thromboses of hepatic arteries, to our knowledge, have not been recorded. Yater and Mollari[23] described in detail a clot in the hepatic artery but admitted that it was probably formed after death. Thrombi in renal arteries are, likewise, not described, though scars in the cortex are frequently referred to as healing infarctions (Graham,[9] and others) without evidence of thrombosis. We have not been able to find reference to thrombi in arteries of other organs though they are frequently mentioned in general statements.

Thus, the search for arterial thrombi in sickle cell disease yielded surprisingly few conclusive reports, particularly when one takes into account the efforts which have been made to explain their pathogenesis.

Stasis (due to capillary blockade and vasodilatation), endothelial damage (due to anoxia), and an increase of coagulating bodies in the circulating blood have been held responsible for the supposedly frequent occurrence of vascular thrombosis in sickle cell disease. The existence of capillary stasis cannot be questioned. Capillary thromboses may also occur, although in many reports in which they have been specifically mentioned, they have been seen within areas of necroses. The description of such thrombi is often inconclusive, and Wertham, Mitchell and Angrist[21] stated that many of them, in their cases, were probably agonal. Most authors imply that the thrombi result directly from stasis, although our present knowledge of the pathogenesis of thrombosis requires additional precipitating factors. Murphy and Shapiro[14] refer to the experimental work of Pennell[16] who demonstrated that disintegration of platelets is the result of their conglutination with red blood cells. Pennell, however, in his experiments and conclusions referred to "shed blood." We still have no evidence that intravascular stagnation of blood flow alone without endothelial damage or changes in the coagulating properties of the blood leads to thrombosis.

Capillary thromboses at any rate are of relatively minor importance inasmuch as their occurrence is not consistent and inasmuch as they cannot bring about the massive foci of necroses in brain, spleen, kidney and liver, which are being discussed. In order to explain these, thrombi in respectively large arteries must be demonstrated or vascular spasm may be assumed.

As pointed out before, ischemic infarctions have been described more often without than with related thrombi. Furthermore, cases of sickle cell disease have been put on record and have been quoted, in which associated renal disease and hypertension may have been responsible for the vascular lesion (Wertham, Mitchell and Angrist;[21] Hughes, Diggs and Gillespie[12] 'Case 2'). On the other hand, absence of thrombi in large vessels corresponding to the ischemic infarctions have been repeatedly stated (Hughes, Diggs and Gillespie;[12] Wade and Stevenson;[19] Bridgers;[4] and our own case). It can, therefore, be concluded that ischemic infarctions may occur in sickle cell disease with, and perhaps more often without, thrombotic occlusion of arteries.

The cause of thrombosis of large arteries, if it occurs, has, as yet, not been satisfactorily explained. Murphy and Shapiro[14] assume that stasis leading to thrombosis causes liberation of coagulating bodies into the circulation, thus accounting for thrombosis of larger vessels. Their own observations, however, regarding the prothrombin time in their case of sickle cell crisis show prolonged prothrombin time, heralding the approach of crisis, returning to "slightly below normal." It appears to us that these limited findings do not constitute a safe basis on which arterial thromboses can be explained.

In the absence of thrombotic vascular occlusion, fat emboli have been thought of as playing a part in bringing about parenchymatous necroses. Wade and Stevenson,[19] and Wertham, Mitchell and Angrist[21] did not find changes in the bone marrow. The significance of so-called fat emboli remains questionable. In the first place, Wertham, Mitchell and Angrist[21] did not find them consistently correlated to the foci of necrosis in the brain and, in the second place, they would hardly account for large wedge-shaped infarctions. In our case, we were unable to find fat in the capillaries of the brain.

Finally, *endarteritis* has repeatedly been described and postulated as the primary cause of parenchymatous damage. Endothelial proliferation with or without hyalinization of arteriolar walls has been observed several times in the brain and occasionally in the spleen. Bridgers[4] noted obliterating endarteritis in the brain of 1 of his cases; Yater and Hansmann[22] report obliterating thromboangiitis of the lung with hypertrophy of the right heart in 1 case. The findings of true obliterating endarteritis cannot be regarded as an essential pathologic feature in sickle cell disease since they have been observed only exceptionally. In view of the relative frequency of sickle cell disease in the colored race and the extreme rarity of true endarteritis, the correlation appears to be coincidental rather than causative.

Comment. If we confine ourselves to such pathologic observations that have been consistently reported in cases of uncomplicated sickle cell disease, we find that little has been added since the presentation of this subject by Diggs and Ching[6] in 1934. The many varieties of morphologic changes, however, are still not satisfactorily correlated. One group of phenomena revolving around the hemolytic anemia includes the siderofibrosis of the spleen, hemosiderosis of liver and kidneys (Stasney[17]), the relative frequency of gall stones (Weens[20]), the hematologic changes in the peripheral blood as well as in the bone marrow. The initial enlargement of the spleen and its subsequent atrophy and fibrosis may also belong to this group, although the pathogenesis of this process is not clearly understood.

The second group of phenomena—to which we shall confine our comments—concerns circulatory disturbances. Ische-

mic necroses of inner organs, though frequently observed, are not consistently found. They may or they may not be associated with organic changes in the vascular tree. Degenerative changes in the vessel walls, endarteritis, thrombosis, and fat emboli have been described. The greatest handicap in the evaluation of these findings lies in the still relatively limited number of postmortem examinations. Not all of the previous reports permit a clear concept of the relationship between the vascular lesions and the sickle cell disease. It has been repeatedly suspected that coincidental diseases might actually have been the cause of vascular changes.

In an attempt to correlate most of these phenomena we are inclined to fall back on our own observations, from which we have learned that extensive ischemic infarctions may occur in uncomplicated cases of sickle cell disease without visible organic changes in the vascular tree. The same set of circumstances is encountered in other conditions. The changes in the liver, in our case, simulate closely those seen in severe eclampsia or in shock following extensive burns (Duffin[8]). Cortical necroses of the kidney have often been described in pregnancy and other apparently unassociated conditions. The isolated infarctions of the spleen, kidney and brain have been described as the result of trauma without mechanical vascular occlusion. Neuberger[15] first pointed out that vascular spasm is apparently responsible for such occurrence. We have repeatedly observed ischemic infarctions of kidneys, spleen, small intestine and brain, in posttraumatic cases in which careful gross and microscopic search appeared to exclude satisfactorily a thrombotic occlusion of the responsible artery.

Duff and Murray[7] have compiled the theories concerning the pathogenesis of bilateral renal necrosis and it appears reasonable to us to apply similar thoughts to the ischemic necroses in sickle cell disease. If we suppose that the process is initiated by vascular spasms, it may be assumed that vasodilatation may follow and that the stagnation of blood flow may result in ischemic necrosis of vessel walls, with subsequent thromboses. Depending on the duration of the vascular spasm, the blood flow may be reëstablished at any one of these stages and ischemic infarctions may thus be found with or without thrombosis, with or without the degenerative changes in the vascular wall. Stasis, however, is most commonly found.

Tomlinson[18] finds the clinical signs and symptoms of sickle cell crisis referable to shock associated with rapid destruction of red blood cells. This proposition dovetails readily into the previously mentioned hypothesis of vascular spasm as the initiating factor leading to parenchymatous necroses.

The clinical record of our own case, as that of many others, shows typical sickle cell crisis but does not indicate an actual state of shock prior to the laparotomy. The laboratory data, however, are not sufficiently complete. The patient was not examined for relative hemoconcentration and the plasma protein level was not determined. Actual shock was precipitated by the operation and it is likely that the blood pressure during the sickle cell crisis was maintained by peripheral vascular spasm, assumed to occur during the pre-shock stage.

The sequence of events, as we see it at this time, presents itself as follows: 1. Accepting Tomlinson's theory as a working hypothesis, the sickle cell crisis constitutes an equivalent to pre-shock or shock. The crisis may be initiated by various factors which produce a decrease of oxygen in the peripheral blood. It is characterized by rapid blood destruction and an obviously mounting diminution of the oxygen-carrying capacity of the red blood cells. The mere fact that the erythrocytes are sickled proves that they do not carry sufficient oxygen. In accordance with our present concept, peripheral vascular spasms may at least temporarily maintain normal blood pressure, but it will also increase tissue anoxia, leading to

further sickling and to the introduction of a vicious cycle.

2. The peripheral vascular spasm may lead directly to ischemic necrosis in inner organs or may be followed by capillary dilatation or stasis. During this phase of failure of peripheral circulation the capillaries are "engorged" and "packed" with sickle cells. We regard this phenomenon as a result rather than the cause of capillary stasis.

3. Local ischemia of tissue and capillary walls may result in organic damage to the vessel walls, degenerative changes, thrombosis, resulting further in superimposed infarctions.

We are presenting this hypothesis as a plausible explanation of the multitude of findings, all of which can be traced directly to various phases of one and the same process. It explains the frequent reports of ischemic infarctions without vascular thrombosis, as well as the occurrence of thrombi. It eliminates the concept of primary capillary blockage which cannot be correlated to gross infarctions without assuming an unrelated process in larger vessels.

Summary. 1. A case of sickle cell disease is reported in which cholecystectomy in sickle cell crisis resulted in death of the patient.

2. Multiple large foci of ischemic necrosis were observed in inner organs. The changes in the brain resembled those of Schilder's encephalitis, those in the liver simulated the changes in eclampsia, those in the kidneys bilateral cortical necrosis.

3. No organic changes in the vascular tree were observed. Thrombi, in particular, were absent.

4. A review of the literature in contrast to the current opinion reveals the inconsistency of vascular changes, thromboses and the lack of correlation between parenchymatous necroses and mechanical vascular occlusions.

5. A theory is presented intending to correlate the multitude of morphologic findings with particular reference to ischemic infarctions of inner organs in sickle cell disease.

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AN EVALUATION OF THENYLENE HYDROCHLORIDE [N,N-DIMETHYL-N′-(ALPHA-PYRIDYL)-N′-(ALPHA-THENYL) ETHYLENEDIAMINE HYDROCHLORIDE]

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Diphenhydramine hydrochloride (benadryl hydrochloride or beta-dimethylaminoethyl benzhydryleth erhy drochloride) and tripelennamine hydrochloride (pyribenzamine hydrochloride)or N,N-dimethyl -N′-benzyl-N′-(alpha-pyridyl) ethylenediamide hydrochloride are now being used extensively as adjuncts to the therapeutic armamentarium in the treatment of dermatoses characterized by pruritus, especially those with cutaneous edema, such as urticaria and angioneurotic edema. Our study was undertaken in order to evaluate thenylene hydrochloride [N′,N-dimethyl - N′ - (alpha - pyridyl) - N′ - (alpha-thenyl) ethylenediamine hydrochloride], a new addition to the group of antihistamine drugs. We wish to record our experience with its therapeutic efficacy in dermatologic conditions, its untoward reactions, and an incidental observation of the relative merits of the 3 drugs, thenylene, benadryl and pyribenzamine.

Thenylene hydrochloride is a white crystalline material possessing antihistamine qualities. It is non-hygroscopic but readily soluble in water. Studies by the originators of the drug (Abbott Laboratories) on isolated portions of the ileums of guinea pigs and intestines of rabbits have shown that thenylene has definite activity in preventing or abolishing spasm produced by histamine. In animals it has a negligible effect on blood pressure when given intravenously in doses of less than 1 mg. per kg. of body weight.

Data on 126 patients treated with thenylene at the Mayo Clinic will be presented in this report. Thenylene has been used in the treatment of additional patients, but sufficient observations have not been made on them to allow inclusion of this part of our experience in this preliminary report. The 126 patients concerning whom we are reporting had a variety of dermatologic conditions. About 50% were hospitalized during at least part of our observation and about 50% were seen as out-patients only. All of the patients received regular dermatologic care, such as application of soothing lotions, ointments, wet dressings and so forth. This fact renders a statistically valid report impossible, but we have attempted in so far as possible to evaluate the patient's reactions to the antihistamine drugs studied. All of the patients received thenylene; 39 received both benadryl and pyribenzamine in addition to thenylene; 8 received benadryl and thenylene, and 5 received pyribenzamine and thenylene. The dosages used varied but in general benadryl and pyribenzamine were given by mouth in doses of 50 mg. 3 or 4 times a day and thenylene in doses of 100 mg. 3 or 4 times a day. No patient received treatment with more than 1 of these drugs at a time.

The observations are summarized in Tables 1 to 5. The responses have been classed arbitrarily into 3 categories: definite improvement, slight improvement and no improvement. In most cases pruritus was the symptom which responded to treatment. In the cases of urticaria and angioneurotic edema relief or im-

provement was indicated by lessening or abolition of edematous wheals or plaques as well as cessation of the pruritus. In the cases of dermatitis venenata and eczema improvement meant not only partial or complete relief from pruritus but in some cases the drugs seemed to hasten the resolution of vesicular dermatitis. It is not possible to separate the rôle of local and general supportive treatment from that played by the drugs under consideration. In our data many dermatoses were represented, but for the sake of simplicity and because the number of cases in the different categories was for the most part so small, many cases were included in the group called "miscellaneous conditions." The miscellaneous group consisted of cases of dermatitis venenata, exfoliative dermatitis of unknown etiology, mycosis fungoides, dermatitis herpetiformis, subacute disseminated lupus erythematosus, erythema nodosum, secondary sensitization dermatitis due to overtreatment and others.

The data regarding the 126 patients who received thenylene are summarized in Table 1. In all, 86 (68.2%) gained some degree of relief. For certain of the conditions little was anticipated from the use of this drug. For atopic dermatitis the main effect anticipated was some relief from the paroxysms of pruritus which usually accompany this condition. Of the 28 patients who had atopic dermatitis, 18 obtained varying degrees of relief. On the other hand 10 of these patients felt the drug was ineffective in ameliorating the pruritus. It is noteworthy that those who had urticarious lesions, whether acute or chronic, gave the most satisfactory response. In the urticaria and angioneurotic group were cases in which the etiology was known as well as some in which it was unknown. Four out of 5 patients who had anal or vulval pruritus were helped. In the miscellaneous group the best response was obtained in cases of acute dermatitis venenata.

Of the patients, 47 were given benadryl as well as thenylene (Table 2); 33 (70.2%) were benefited by use of benadryl. Of the 44 patients who received pyribenzamine, 24 (54.5%) were helped (Table 3).

The proportion of patients in the 4 diagnostic categories of Tables 1, 2 and 3 are roughly the same. The tables, therefore, lend themselves to a rough comparison of responses obtained. It should be pointed out that although some patients received all 3 drugs, all did not. The patients were not chosen for this study in any particular way. They were seen by different physicians who had available 3 preparations, thenylene, benadryl and pyribenzamine. The observations are thus those of the patients and the various physicians who frequently prescribed 1 preparation and tried another only if 1 of the others failed to help. Certainly no statistically valid conclusions can be drawn, yet the material is extensive enough to allow clinical observations of the effects of these drugs.

Comparison of the results of use of the 3 drugs revealed that 70.2% of the patients objectively showed or subjectively felt improvement from use of benadryl, 68.2% from use of thenylene, and 54.5% from use of pyribenzamine hydrochloride. The response varied markedly in the different groups by diagnostic classification. In cases of urticaria and angioneurotic edema the objective change following treatment, namely, decrease in size or disappearance of the wheals, could be observed best. Also the condition is definitely one resulting from extravasation of fluid which causes localized edema and thus is directly responsive to anthistamine preparations. As expected, all of the drugs showed the most marked activity in this group. Out of 25 patients, 22 were helped with thenylene, 7 out of 9 with benadryl, and 6 out of 7 with pyribenzamine. Thus in our experience for a condition responding to the direct antihistamine properties of the drugs all 3 were of relatively equal value.

Of 28 patients, who had atopic dermatitis 18 felt that thenylene gave them relief from pruritus, while 12 of 14 and

TABLE 1.—THERAPEUTIC EFFECTIVENESS OF THENYLENE

Diagnosis	Degree of improvement (cases)			Total cases
	Definite	Slight	None	
Atopic dermatitis	11	7	10	28
Eczema*	11	17	11	39
Urticaria and angioneurotic edema	19	3	3	25
Miscellaneous conditions	9	9	16	34
Total	50	36	40	126

* Other than classical atopic dermatitis including; multiple lichen simplex chronicus, nummular eczema, exudative neurodermatitis, and so forth.

TABLE 2.—THERAPEUTIC EFFECTIVENESS OF BENADRYL

Diagnosis	Degree of improvement (cases			Total cases
	Definite	Slight	None	
Atopic dermatitis	7	5	2	14
Eczema*	6	4	5	15
Urticaria and angioneurotic edema	7	0	2	9
Miscellaneous conditions	1	2	6	9
Total	21	11	15	47

* Other than classical atopic dermatitis including: multiple lichen simplex chronicus, nummular eczema, exudative neurodermatitis, and so forth.

TABLE 3.—THERAPEUTIC EFFECTIVENESS OF PYRIBENZAMINE

Diagnosis	Degree of improvement (cases)			Total cases
	Definite	Slight	None	
Atopic dermatitis	2	4	6	12
Eczema*	4	5	5	14
Urticaria and angioneurotic edema	6	0	1	7
Miscellaneous conditions	1	2	8	11
Total	13	11	20	44

* Other than classical atopic dermatitis including: multiple lichen simplex chronicus, nummular eczema, exudative neurodermatitis, and so forth.

TABLE 4.—PATIENTS PREFERRING A CERTAIN DRUG

Diagnosis	Thenylene	Benadryl	Pyribenzamine	Total patients	
				With preference	Taking all 3 drugs
Atopic dermatitis	2	3	3	8	12
Eczema*	3	1	0	4	13
Urticaria and angioneurotic edema	4	0	0	4	6
Miscellaneous	1	0	0	1	8
Total	10	4	3	17	39

* Other than classical atopic dermatitis including: multiple lichen simplex chronicus, nummular eczema, exudative neurodermatitis, and so forth.

TABLE 5.—UNTOWARD REACTIONS WITH THENYLENE

Symptom	No. reactions
Drowsiness	10
Dizziness	5
Vomiting and gastro-intestinal upset	5
Headache	3
Insomnia	1
Nervousness	1
Urinary difficulty	1
Bitter taste in mouth	1

6 of 12 felt benadryl and pyribenzamine, respectively, helped them. Here the patient's subjective valuation is paramount. The greater sedative effect of the benadryl probably accounts for its better showing. Patients with atopic dermatitis benefit generally from sedation and on direct questioning several of this group stated that they preferred benadryl to the others because of its greater quieting effect on them generally.

Thirty-nine patients received treatment with all 3 drugs at different times. Only 17 of this group expressed a definite preference for 1 preparation over the others. These preferences are listed in Table 4. This table is based entirely on the preferences of the patients. Although the patients who received treatment with all 3 drugs represent only a part of the whole group, it is somewhat surprising that the apparent superiority of benadryl in atopic dermatitis, as previously mentioned, is not evidenced by this group. Untoward reactions understandably figured largely in the patient's comparison of the drugs.

Untoward reactions to thenylene are listed in Table 5. A patient sometimes had more than 1 reaction. If such was the case each symptom has been noted so that in this table the number of times each reaction was experienced by the entire group is given rather than the number of patients in the group who noted reactions. Ten of the 126 patients, taking thenylene, complained of drowsiness as did 3 of the 47 taking benadryl, and 1 of the 44 taking pyribenzamine. For the most part drowsiness when it occurred with benadryl was more marked than with either of the other drugs and relatively more patients who were taking benadryl experienced a slight sedative effect not classified as an untoward reaction. A patient who had benign prostatic hypertrophy had increased difficulty in voiding while he was taking thenylene, and he also experienced the same difficulty during treatment with both benadryl and pyribenzamine. The aggravation of the difficulty ceased with discontinuance of use of these drugs. In our group no serious toxic reactions were experienced although it was necessary to stop medication in several cases. Patients intolerant to one drug frequently could tolerate another. No cumulative effects were noted. Bromsulfalein tests of liver function were conducted on 4 of the patients who had taken thenylene in daily doses of from 0.3 to 0.4 gm. for 9, 17, 36 and 43 days, respectively. There was no retention of dye in any of these cases.

Summary and Conclusions. A clinical evaluation of thenylene, a new drug with antihistamine properties, shows it to be of definite value in treatment of certain dermatologic conditions. Its most marked effect was in treatment of dermatoses, such as urticaria and angioneurotic edema which are characterized by cutaneous edema. With few exceptions oral doses of from 50 to 100 mg. 3 or 4 times a day led to lessening or disappearance of such edema. No cumulative effect was noted and untoward reactions were minimal. A clinical comparison of the results of treatment with thenylene, benadryl and pyribenzamine revealed a high degree of similarity

ECCHYMOSIS OF THE ABDOMINAL WALL AS AN EARLY DIAGNOSTIC SIGN OF DISSECTING ANEURYSM OF THE AORTA

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Acute dissecting aneurysm of the aorta is seen rather infrequently. At the Massachusetts General Hospital 30 such cases were seen from 1897 to 1946,[2] and of these 30 cases, a correct antemortem diagnosis of dissecting aneurysm of the aorta had been established in 10.

It is not the purpose of this communication to reëmphasize the clinical picture, nor to enumerate the symptoms and signs. These have been admirably done in literature and text. Rather it is concerned with the reporting of an observation heretofore not described or reported in the literature reviewed. It was of sufficient significance to establish a diagnosis of acute dissecting aneurysm of the aorta at a time when the clinical diagnosis seemed to be iliac embolism, and when the idea of operative interference was entertained. The literature contains reports of cases in which operative relief was attempted for supposed iliac thrombosis or embolism in which the phenomena associated with the latter were really a part of the picture of acute dissecting aneurysm of the aorta.[2,3]

Clinical Abstract. A white female, aged 52, without a history of previous illness or trauma, suddenly had severe non-radiating chest pain, followed in a few moments by lower abdominal pain, and shortly thereafter by pain in the left leg. She then noted numbness and tingling, and inability to move the leg. Examination 1 hour after the onset showed the pulse to be slow and regular. The blood pressure was 158 (systolic) and 68 (diastolic), measured in mm. of mercury. The heart sounds were distant. There was pallor of the left leg, and it felt colder to the touch than did the right leg. There was absence of sensation to touch and pin. There was almost complete inability to move the leg. Femoral pulsation was absent on the left but present on the right side. The symptoms and findings, namely pallor, lowered surface temperature, loss of sensation and muscle power, and absence of pulsation in the arteries of the involved extremity, were typical of those found in embolism of the femoral or iliac arteries. Within one-half hour there appeared an area of purplish discoloration, about 10 cm. in diameter, in the skin of the left lower abdominal quadrant. The presence of this area of ecchymosis suggested the likelihood of the iliac obstruction being merely a part of a more extensive process; and that the ecchymosis represented bleeding from the left deep inferior epigastric artery. A diagnosis was thus made of a dissecting aneurysm of the aorta with involvement of the iliac artery and the deep inferior epigastric artery, the latter involvement producing the ecchymosis. Several hours later an area of ecchymosis appeared in the skin of the right lower abdominal quadrant. The patient had not voided for some 20 hours, and although the bladder was not distended, it was catheterized, 15 cc. of non-bloody urine being obtained. Since subclinical shock was not manifest for some hours after the onset, it was felt that the shock did not contribute entirely to the anuria, but that the renal arteries were involved in the dissecting process. Similarly, the stools contained fresh blood, suggesting involvement of the inferior mesenteric artery.

The patient became increasingly restless and cyanotic (the usual supportive therapy was given throughout, including transfusions of plasma and whole blood, oxygen, etc., and

*This department is in part supported by the Michael Reese Research Foundation.

died 30 hours after the onset of the initial symptoms.

AUTOPSY. (Only the most important findings shall be mentioned.) The purplish discoloration which had been noted clinically was present in the skin over the lower abdominal quadrant. The subcutaneous tissue and the adjacent muscles also disclosed foci of hemorrhages. The peritoneal cavity contained approximately 1000 cc. of yellowish, slightly hemorrhagic, but otherwise clear liquid. Foci of hemorrhages were present just beneath the peritoneum of several loops of small intestine. The heart with the attached pericardium weighed 450 gm. The epicardium was covered with small fibrinous excrescences beneath which a number of minute hemorrhages were noted. These hemorrhages were particularly pronounced at the base of the heart and along the course of the coronary arteries. The ascending and descending aorta when inspected before opening, appeared purplish gray. The valvular apparatus was intact. The left ventricular wall measured about 13 mm. in thickness; the right, 3 mm. A number of subendocardial hemorrhages were noted in the right auricle and right ventricle. The myocardium was firm and reddish brown. Moderate to severe arteriosclerosis was found in both coronary arteries. Their lumens were patent. The aorta throughout its length, the proximal portions of the great vessels of the neck, the common and external iliac arteries and femoral arteries resembled a double barreled tube. The adventitia and media were separated by a moderate amount of partially liquid and clotted blood. Within the ascending aorta about 2 cm. above the anterior cusp of the aortic valve there was a Y-shaped ragged tear in the intima. This tear was present in an atheromatous ulcer which measured about 0.8 x 2 cm. in its greatest diameter. The surrounding intima was calcified and undermined by hemorrhagic material. The tear within the base of the ulcer communicated freely with the space between the media and adventitia of the aorta. The tear also communicated with various subepicardial spaces.

The dissection had extended into the femoral arteries and from there cranially along both inferior epigastric arteries. The dissection also involved both renal arteries and the mouth of the inferior mesenteric artery.

A number of hemorrhages were found throughout the mucosa of the transverse and descending colon, but were most pronounced in the sigmoid and rectum.

Microscopic examination of the aorta disclosed severe arteriosclerosis and a number of typical atheromatous ulcers. Nowhere was any evidence of syphilis or medial necrosis observed.

SUMMARY. At the autopsy of a 52 year old white female, marked arteriosclerosis and atheromatosis of the aorta was present with formation of atheromatous ulcers. One of these, located in the ascending aorta just above the aortic valve, had ruptured through to the media and caused a large dissecting aneurysm extending along the ascending aorta, arch, and descending aorta. From there the hemorrhage had extended along both inferior epigastric arteries and had produced a subcutaneous hemorrhage in the region of the lower abdominal quadrant.

Discussion. In this case of dissecting aneurysm of the aorta there was present an unusual clinical sign heretofore undescribed.[1-4] The immediate clinical picture was one of left iliac embolism, and surgical intervention was entertained. However, by virtue of the area of ecchymosis in the skin of the lower abdomen, it was felt that what first appeared to be a left iliac obstruction was merely a part of a more extensive process, and that the patient had a dissecting aneurysm, involving among other vessels the external iliacs, and extending on through the deep inferior epigastric arteries. Surgical intervention was thus obviously not undertaken. Autopsy revealed the anticipated involvement.

Conclusions. In a patient with findings indicative of acute embolic occlusion of the iliac artery, the presence of ecchymosis of the abdominal wall suggested the diagnosis of acute dissecting aneurysm of the aorta, the ecchymosis resulting from involvement of the deep inferior epigastric arteries. Pathologic studies confirmed this. To our knowledge, this observation has not been previously recorded.

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THE CLINICAL USE OF A TRIPLE SULFONAMIDE MIXTURE

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One of the greatest advances in the use of sulfa drugs is unquestionably the recent introduction of multiple sulfonamide therapy. The investigations by Frisk, Hagerman and co-workers[3,4,5] and by Lehr[7] have shown that the solubility of a given sulfa drug in plasma and urine is practically not affected by the presence of other sulfonamides. Thus all the undesirable side reactions which are due to the rather low solubility of the various sulfa drugs can be greatly reduced if mixtures of several sulfonamides are given. While most of the clinical work so far has been restricted to combinations of 2 sulfa drugs,[8,10,12] it was only logical to extend this idea to triple sulfonamide mixtures. Such an extension is made possible by the fact that the 3 most commonly used drugs of this group, namely, sulfadiazine, sulfamerazine and sulfathiazole, are quite similar in their antibacterial activity and thus are interchangeable in the majority of conditions requiring this type of therapy. Frisk[4] has reported that such a triple sulfonamide mixture has been used in Sweden "in many hundreds of cases of acute pneumonia with good results and tolerance and without any known cases of renal calculi, also with increased doses in many cases of gonorrhea."

The main interest in multiple sulfonamide therapy has centered around the reduction of renal complications, particularly crystalluria. The latter has been reported to be present in from 26 to 28% when administering sulfadiazine or sulfamerazine alone.[1] It can be reduced to 6% when a combination of 2 drugs, sulfadiazine and sulfamerazine, is used,[1] and it can be further reduced to below 3% when adequate amounts of systemic alkalizers are added to a mixture of 2 sulfa drugs.[12]

In the present study, we have extended our investigation of multiple sulfonamide therapy to the use of a mixture consisting of sulfadiazine, sulfamerazine and sulfathiazole without any alkalizing salts. The preparation was composed of: sulfadiazine (microcrystalline), 3.5% (wt. vol.); sulfamerazine (microcrystalline), 3%; and sulfathiazole (microcrystalline), 3.5%; in an aromatized aqueous suspension base.* The reason for supplying smaller proportions of sulfamerazine was due to the fact that this drug is excreted at a slower rate than the other 2 components and is, therefore, needed in smaller amounts.

The preparation was given to 28 unselected patients mostly surgical cases requiring sulfonamide therapy. The initial dose was from 20 to 40 cc., representing from 2 to 4 gm. of total sulfonamides followed by 10 cc. = 1 gm. of total sulfonamides every 4 hours. Blood samples were taken repeatedly during the treatment and urine specimens were collected from each voiding. The group consisted of 18 men and 10 women ranging in age from 16 to 74 years. Altogether 101 blood and 218 urine specimens were obtained and in all samples the concentration of free and total sulfonamides was determined. In addition all urine specimens were inspected microscopically for sulfa crystals (free and acetylated), and, when present, the crystals were identified by a qualitative chemical test.

The average blood concentration was

found to be 7.8 mg. of free and 8.5 mg. of total sulfonamides. These figures represent exactly the values which could be expected from the known average blood levels for each of the 3 sulfonamides if one considers their relative proportions in the medication. Thus it can be concluded that the absorption of each sulfonamide is not interfered with by the presence of the other components. This is in full accord with earlier observations by Oettinger and Cronheim[12] on dual sulfonamide mixtures.

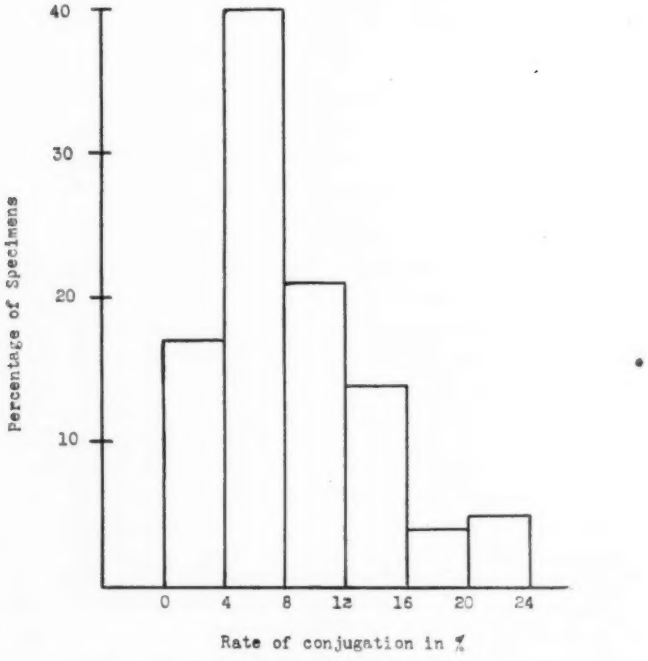

FIG. 1.—Acetylation of sulfonamides in Blood.

The figures also indicate that the acetylation of the sulfonamides in the blood is remarkably low, with an average of 8%. A more detailed distribution is shown in Figure 1. It can be seen that in more than half of all samples the amount of acetylated sulfonamides did not exceed 8%.

From a clinical standpoint, the attained blood levels were fully satisfactory, as evidenced by the fact that the patients responded to the sulfonamide therapy in the usual manner. In some instances, the preparation was given prophylactically while in most instances it was used as specific treatment. Penicillin in conjunction with the sulfonamide mixture was administered to approximately one-half of the patients. No serious side-effects were observed. In no case was it necessary to discontinue the drug. One patient complained of nausea throughout the course of therapy.

The urinalysis showed that over 80% of the specimens had an acid reaction. Unfortunately, it was impossible for technical reasons to make accurate pH determinations or measure the total urine volume for complete excretion studies. However, the concentration of free and total sulfonamides could be determined in all specimens, thus giving accurate data for the degree of acetylation in urine. The figures indicate that an average of 83% of the excreted sulfonamide is in the free form. A more detailed breakdown on the data is presented in Figure 2. It shows that in about two-thirds of all urine specimens less than 20% of the ex-

creted sulfonamides were in the conjugated form. This indicates a lesser degree of acetylation than has been reported for single sulfonamides (Table 1).

The total number of urine specimens containing sulfa crystals was 6, corresponding to 3%. Three of these specimens were from 1 patient who during a previous illness had shown an unusual susceptibility to sulfa drugs. The other 3 samples were from 3 different patients. In each case the crystals were so few that they did not require interruption of the treatment, and were not found in subsequent urine samples.

Discussion. It is generally agreed that the main limitation in sulfonamide therapy has been the danger of kidney damage from the precipitation of the free or conjugated drug. While it is possible to reduce this danger by the simultaneous administration of alkali the amounts required to be effective are so great that they cannot be used indiscriminately for several reasons: they might lead to alkalosis, they present an additional load on the gastro-intestinal tract and the kidneys, and they are definitely contraindicated in patients with renal or cardiac insufficiency. In addition, large amounts

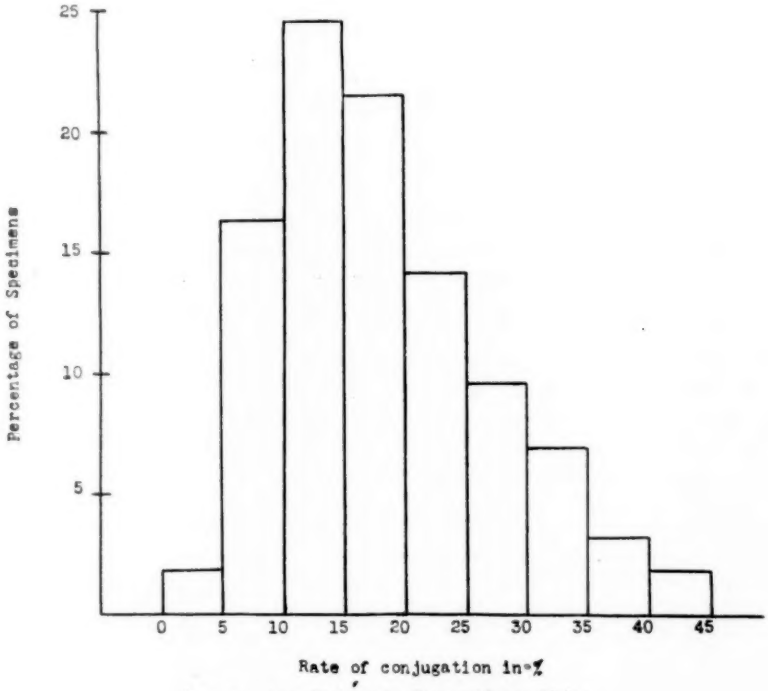

FIG. 2.—Acetylation of sulfonamides in Urine.

TABLE 1.—DEGREE OF ACETYLATION (%)

Drug	Blood	Urine	Reference
Sulfadiazine	10	30	Wheeler[16]
	14	30	Reinhold[14]
	16	..	Flippin[2]
Sulfamerazine	11–18	Over 40	Murphy[11]
Sulfathiazole	12	14	Sadusk[15]
	24	26	Reinhold[13]
	28	..	Flippin[2]
Triple sulfonamide mixture	8	17	Present investigation

of alkali depress considerably the blood concentration of sulfonamides[6] and thereby reduce the efficacy of the medication.

All these dangers are avoided when multiple sulfonamide therapy is used. Table 2 summarizes how the incidence of crystalluria is reduced. The figures clearly indicate the superiority of sulfonamide mixtures.

fonamides are conjugated responds, not to the total concentration of circulating sulfa drugs, but "processes" each sulfonamide as a separate chemical compound in accordance with its low individual concentration. Whatever the explanation might be, the fact that there is less acetylation should make multiple sulfonamide therapy more efficient since only

TABLE 2.—CRYSTALLURIA IN SULFONAMIDE THERAPY

Drug given during 24 hour period	Crystalluria (%)	Reference
4–6 gm. sulfadiazine	28	Flippin[1]
4–6 gm. sulfamerazine	26	Flippin[1]
4–6 gm. sulfadiazine + sulfamerazine	6	Flippin[1]
4 gm. sulfadiazine + sulfathiazole + systemic alkalizers equivalent to 6.6 gm. of sodium bicarbonate	3	Oettinger and Cronheim[12]
4 gm. sulfadiazine + sulfamerazine + sulfathiazole	3	Present investigation

It should be pointed out that multiple sulfonamide mixtures not only reduce the incidence of crystalluria, but have other advantages which might prove to be equally important. Due to the greater tolerance of this type of preparation, it is possible to increase the total dose of sulfonamides so as to obtain higher blood levels. This is desirable not only in certain types of infections such as meningitis, where the drug has to cross the hematocephalic barrier and pass into the cerebrospinal fluid, but also in cases where the pathogenic organisms show an increased resistance to sulfonamides.

Another factor in favor of multiple sulfonamide therapy is the low rate of acetylation which has been found in this and earlier studies.[8,10,12] This applies to both blood and urine as can be seen from a comparison of the data presented in Table 2. The observations seem to indicate that the mechanism by which sulfonamides are conjugated responds, not to the total concentration of circulating sulfa drugs, but "processes" each sulfonamide as a separate chemical compound in accordance with its low individual concentration. Whatever the explanation might be, the fact that there is less acetylation should make multiple sulfonamide therapy more efficient since only the free form of the sulfa drugs has a bacteriostatic action. This view is in full accord with the observations by Lehr and his co-workers who emphasized repeatedly the rapidity of the therapeutic response to mixed sulfonamides.

Summary. A mixture containing sulfadiazine, sulfamerazine and sulfathiazole in microcrystalline suspension has been studied with regard to absorption, excretion and crystalluria.

Adequate blood levels are maintained on the usual dosage schedule of from 2 to 4 gm. of total sulfonamides initially followed by 1 gm. every 4 hours.

The incidence of crystalluria is extremely low even though no alkali was administered in any form. In no case was it necessary to discontinue drug treatment.

The acetylation of the sulfonamides in both blood and urine seems to be noticeably reduced.

* This preparation was supplied by the S. E. Massengill Company, Bristol, Tennessee.

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CHOLESTEROL METABOLISM: BLOOD SERUM CHOLESTEROL AND ESTER LEVELS IN 200 CASES OF ACUTE CORONARY THROMBOSIS*†

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The role of fat in the diet has recently aroused widespread interest as to its effect in producing atherosclerosis, arteriosclerosis, and by the same token, coronary artery disease. This report is the first in a series by the authors as a study in the role of the diet (particularly its fat component) the liver, blood plasma colloid disturbances, and the reticuloendothelial system in causing coronary artery disease and systemic arteriosclerosis.

Contradictory reports exist on the relationship of the blood cholesterol to atherosclerosis, coronary artery sclerosis and arteriosclerosis. Some authors report hypercholesteremia in these diseases and others report normal blood cholesterol levels. We believe that these discrepancies may be accounted for by differences in variable technical procedures, sex and age variations, uncontrolled dietary habits during the study and clinical diagnosis of the disease subject to marked variability in interpretations by the various authors.

It has been pointed out[3] that the blood serum cholesterol and the cholesterol ester are constant in normal subjects and are accurate gauges of the blood lipid level. We therefore used the blood serum cholesterol and ester as an index of blood lipid concentration. If the fat in the diet should raise the blood lipid level the blood cholesterol and ester would correspondingly rise.

Certain recent reviews dealing with the etiology of coronary artery disease have ascribed considerable significance to disturbances in cholesterol metabolism[6,10,12]. This concept was originally proposed by Virchow[15] and by Aschoff[2] and was known as the Imbibition Theory[15]. This theory assumes that lipids from the plasma are absorbed directly through the endothelium into the intima and under certain conditions cholesterol and cholesterol esters are deposited there. Virchow believes that first the connective tissue ground substance of the arterial intima had to be weakened by mechanical strain. Aschoff emphasized the importance of increased blood concentrations of cholesterol and esters in atherosclerosis.

Klotz[8] and Leary[9] have advanced the concept of a disordered cholesterol

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metabolism also, but differ from the above theories in their belief that the lipids are brought to the vessel wall by cellular elements essentially within the vessel wall and are deposited there. Leary believes that there is some defense mechanism which removes excess cholesterol from the arteries. The cholesterol esters are transported from wandering "foam" cells to fixed fibroblasts in the arterial wall, thereby resulting in the cholesterol esters found in the vessel walls in arteriosclerosis.

Winternitz[16] has stressed that in atherosclerosis the intimal endothelium is seldom the site of disease; that the vasa vasorum or mural vascular channels in the arteries are the sites of hemorrhages and sclerosis, with later lipid deposition. This theory is not supported by most investigators at present[6].

Hueper[6] has climaxed comprehensive search into the etiology and morphology of arteriosclerosis by concluding that the disease is found exclusively in colloidal disturbances of the lipoids and carbohydrates of the blood plasma. Hueper believes that there exist four fundamental types of anoxemic causative mechanisms in arteriosclerosis: (1) changes causing either hypertonus or hypotonus of the vascular walls; (2) changes in the hydrostatic intravascular pressure, such changes causing hydrostatic hypertension or hypotension; (3) changes in the colloidal plasma composition and resulting equilibrium; these changes involving plasma lipids, proteins and carbohydrates and being both quantitative and qualitative in nature. Thus the exchange of gases and nutritive substances would be disturbed; and (4) changes in the oxygen-carrying power and in the oxygen-carbon dioxide balance of the blood and its tissues.

Anitschkow[1] demonstrated that the atheromatous plaque or typical arteriosclerotic lesion is a deposition of lipids which takes place primarily in the tissue spaces of the arterial intima between the superimposed endothelium and the underlying barrier of the fenestrated internal elastic membrane of the artery.

Various data have been presented in both support and refutation of the above concepts. As stated previously, contradictory results have resulted from variable factors which the present authors have attempted to avoid.

Recent studies appear to lay greater significance on the role of the blood lipids, these including cholesterol and cholesterol esters. It is planned to explore further the role of fat in the diet as the cause of coronary artery disease and arteriosclerosis.

It is well-known that the clinical, electrocardiographic, laboratory and X-ray diagnosis of atherosclerosis and arteriosclerosis are subject to variable interpretation. Only post-mortem or conclusive evidence of acute coronary occlusion is acceptable as a final proof that coronary artery arteriosclerosis is present.

Arteriosclerosis is now the leading cause of morbidity and mortality. Arteriosclerosis, particularly of the coronary arteries is the leading cause of death in the United States of America with a total of 355,000 victims in the 1940 statistics. Joslin[7] calculates the mortality from arteriosclerosis in Massachusetts to be 37% of the total deaths.

The following studies of pre-mortem and post-mortem coronary artery occlusion and its possible relationship to disturbed cholesterol metabolism are therefore presented. This may be of particular importance because of the power of the liver actively to remove cholesterol and fat from the blood, of storing it within its substance[4,12], and of synthesizing and destroying cholesterol.

In view of the conflicting views re-

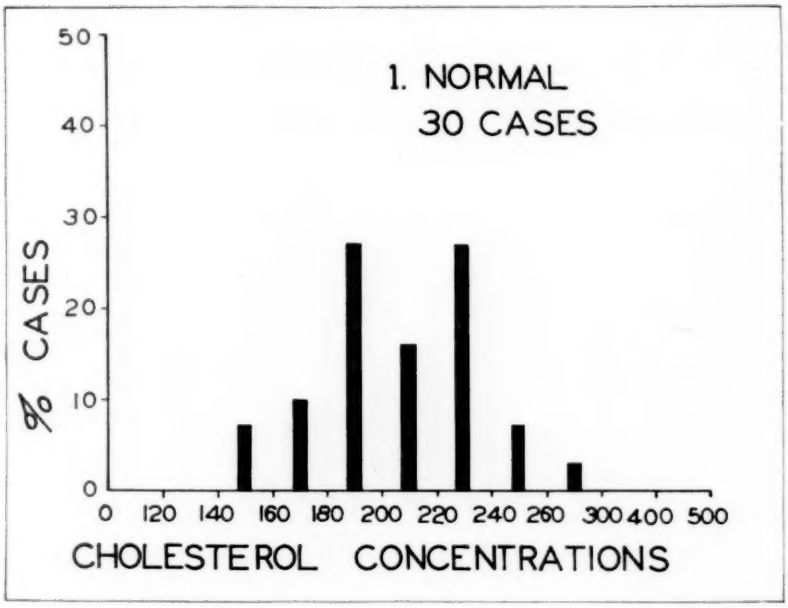
garding the presence of hypercholesterolemia in coronary artery disease, the authors examined a series of 200 cases of acute coronary thrombosis admitted to the wards of the Los Angeles County General Hospital. These cases were all unselected and taken in the order of their admission to the hospital.

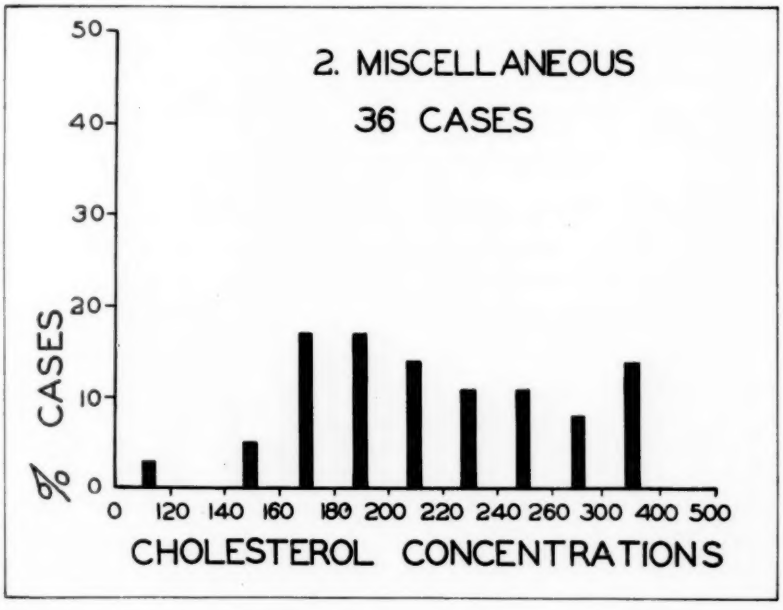
It has been recognised by recent authors that many of the inconsistencies in blood cholesterol determinations have been due to the unreliability of certain methods which have been widely employed. This subject has been adequately reviewed elsewhere [12,14]. Accordingly, a modification of the Sperry-Schoenheimer method has been employed for both cholesterol and cholesterol ester determination. A recent modification has been published by Sperry and Brand[14] and a further modification has been made by one of the authors (A. L. C.) in a method to be published. These modifications have been checked against the original Sperry-Schoenheimer method and also against other procedures in wide use. These results again emphasize the necessity for adherence to the basic principles of the Sperry-Schoenheimer procedure and show that widely varying results may be obtained by other procedures which do not satisfactorily control the Lieberman-Burchard color reaction. The modification used in the series of cases to be presented appreciably shortens the time of determination and reduces the complexities of the original Sperry-Schoenheimer procedure without at the same time sacrificing any of its accuracy.

Clinical Material. Three series of cases are presented here. First, a series of 30 normal controls for comparison with other published series. The second is a series of 36 cases on patients having a wide variety of diseases for comparative purposes. Third, a series of 200 cases of acute coronary occlusion, most of whom survived their initial attack, are analyzed. Included are some cases which were examined post-mortem. The following table shows the distribution of cholesterol values obtained in each series. Table 1 presents a summary of the cholesterol values obtained in the three series of cases. In addition, the average age for each group of cholesterol values is shown for the coronary occlusion series. The cases were 90% Caucassian in race, the remainder being either Negro or other races.

Of the cases of coronary occlusion, 75% were males, 25% females and the ages ranged from 28 to 84. Blood cholesterol levels were taken within 48 hours of admission, following the proven acute coronary occlusion and followed in a large percentage of cases with several subsequent determinations at 2 to 6 week intervals. Each case was definitely diagnosed as one of acute coronary occlusion both by the electrocardiographic report and the clinical examination. Both total and

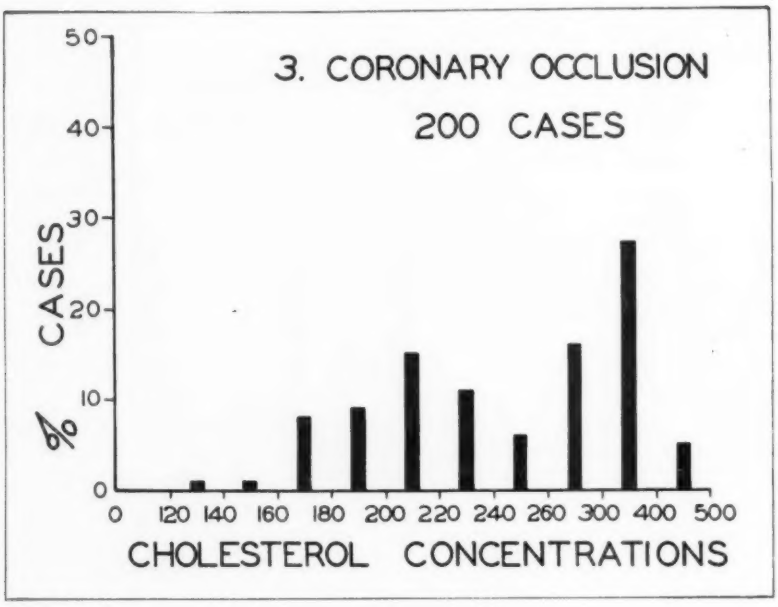
Serum Cholesterol Conc.-Mg/100 cc	Normal Cases	% of Total	Miscellaneous Cases	% of Total	Coronary Occlusion Cases	% of Total	Av. Age
80–139	0	0	1	3	2	1	70
140–159	2	7	2	6	2	1	81
160–179	3	10	6	17	17	8.5	70
180–199	8	27	7	20	18	9	70
200–219	5	17	5	14	31	15.5	65
220–239	8	27	4	11	22	11	61
240–259	2	7	4	11	12	6	61
260–299	1	3	3	8	31	15.5	63
300–399	1	3	5	14	55	27.5	53
400–	..	..	..	..	5	2.5	50
TOTAL	30	100	36	100	200	100	61

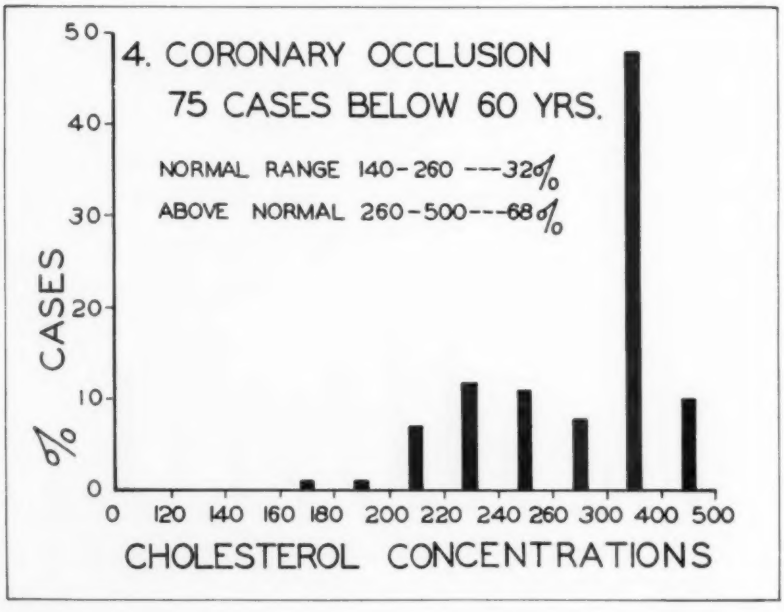




free cholesterol determinations were made on all cases.

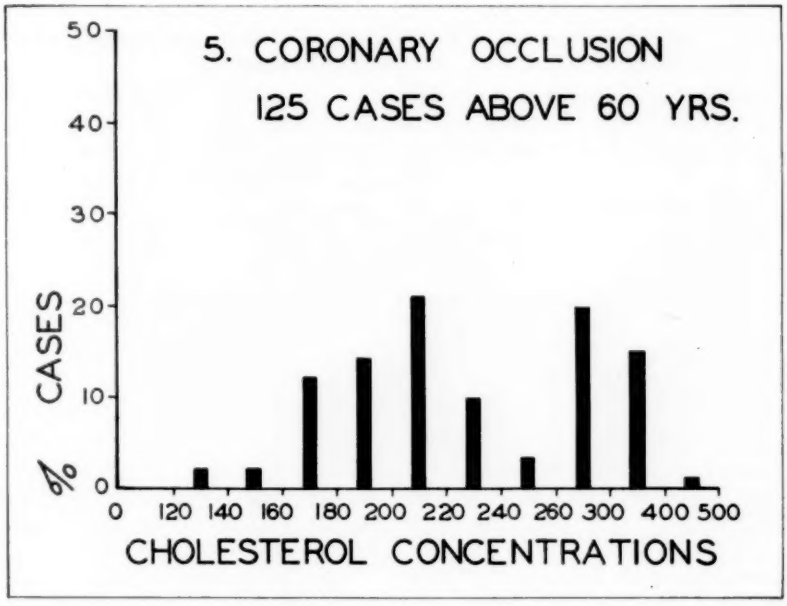
Results. The distribution of cholesterol values is most readily seen in the following series of figures. Figure 1 shows the distribution of cholesterol values for the normal series and it is seen that all but one case, or approximately 97%, are within the range of 150–260 milligrams per 100 cc. This distribution is similar to that published by Peters and Man[11]. The percentage





of free cholesterol ranged from 20 to 35% (average 28%).

Figure 2 shows the distribution of cholesterol values obtained in the miscellaneous series of 36 cases. It may be seen that the distribution here corresponds closely with that of the normal series except for 5 cases with values above the normal range. These cases, incidentally, were all in conditions recognised as being associated with disturbance of cholesterol meta-



bolism, such as biliary cirrhosis, myxedema and diabetes.

The distribution of cholesterol values for the series of coronary occlusion, shown in Figure 3, is seen to be distinctly abnormal. The distribution is such as to indicate a division of the cases into two distinct categories, those in which the cholesterol values are distributed in a normal manner, and an additional class in which the cholesterol concentration is distinctly elevated. It may be concluded from these results that high cholesterol values may be an etiological factor in many cases of coronary occlusion, but other cases occur in which it would appear that cholesterol metabolism may not be involved.

These results are shown even more contrastingly in Figures 4 and 5 in which the cases have been divided according to age. Figure 4 shows a series of 75 cases below the age of 60 and in these it is seen that nearly 70% of the cases have elevated blood cholesterol. In the cases above the age of 60 (Figure 5) this tendency is not nearly so prominent, about 48% being elevated and about 52% in the normal range.

The distribution of cholesterol between the free and the ester form was not markedly changed in this series of cases. The average percent of free cholesterol was 30 compared to 28% in the normal. It does not appear that the mechanism for esterification of cholesterol is involved in this disease entity.

A study of the series with respect to sex distribution does not indicate any marked trend with the exception of the fact that these cases of coronary occlusion were 75% males. The interrelationship of age and cholesterol concentration is also shown in Table 1, in which the average age for each level of cholesterol concentration is given. It is there readily seen that coronary occlusion appears earlier in cases having high cholesterol values.

Summary and Conclusions. 1. A consecutive unselected series of 200 patients with acute coronary occlusion

was studied for blood cholesterol and cholesterol ester levels within 48 hours after hospital admission.

2. In 68% of 75 patients under 60 years of age with proven acute coronary occlusion hypercholesterolemia was present.

3. In 52% of 125 patients over 60 years of age with proven acute coronary occlusion a normal cholesterol level was found.

4. Coronary thrombosis in patients under the age of 60 is frequently associated with hypercholesterolemia and disturbances of cholesterol metabolism.

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PHEOCHROMOCYTOMA OF THE ADRENAL MEDULLA

A Clinicopathological Study of Five Cases

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Pheochromocytoma is a relatively unusual lesion. The present series of 5 cases is one of the largest groups reported from a single institution at any one time, and includes the ninth case on record of bilateral malignant adrenal pheochromocytoma.

Our purpose in this paper is to present several clinical types of pheochromocytoma and to correlate clinical and pathologic findings where this is possible. The different types referred to are: (1) malignant adrenal pheochromocytoma with metastases; (2) benign adrenal pheochromocytoma with hypertension (paroxysmal or sustained); (3) benign adrenal pheochromocytoma found incidentally at autopsy with no clinical signs or symptoms.

General considerations of location of chromaffin tissue, from which these tumors arise and the embryology of this tissue having been adequately discussed[5,10,12] elsewhere will not be considered further here.

In the present series of 5 cases there are 3 males and 2 females. The age incidence varies from 30 to 61 years. Three of the cases occurred between 51 and 61 years of age. The malignant tumor occurred in the 51 year old female. The age and sex incidence of this group is similar to that of previously reported cases.[5]

Association of hypertension with pheochromocytoma is well known.[2,5,9,16,18,20] When hypertension is present the clinical correlation on the basis of present theories is good, *i. e.*, the elaboration of a pressor substance by the tumor cells,[1] causing hypertension which is paroxysmal or sustained. However, there are cases in the literature[12] as well as in the present series, in which this symptom is not present. The absence of hypertension in these cases makes it more difficult to accept the above mechanism as the only one involved.

The details in the case reports below are included only if thought to be connected with the subject under consideration.

Case Reports. Case 1. R. W., a 51 year old white female, was apparently in good health until 2 months prior to admission, when she began to have headaches, chiefly occipital, mild in the morning and more severe later. The patient was dizzy and weak and fell repeatedly during the month before admission. Her memory was poor. She walked leaning to the right and fell frequently for 10 days before admission. During the last week the patient also complained of a stiff neck with increasing drowsiness, and slept almost constantly. There were generalized convulsions on the morning of admission.

Physical Examination. The blood pressure was 160/100. On admission, the patient was drowsy, comatose and did not respond to questions. The pupils were large, irregular and equal and did not respond to light. There was weakness of the left side of the face and rigidity of the neck. The left arm was completely flaccid. The deep reflexes were everywhere diminished, but weaker on the left. The abdominal reflexes were absent and there was no appreciation of pin-prick anywhere. There was bilateral papilledema. The clinical diagnosis was: "rapidly developing intracranial neoplasm, probably in the right frontal area."

Course in the Hospital. On lumbar puncture done on the 2nd hospital day, initial

pressure was 330 mm. (water) and final pressure 114 mm. Ten cc. of bloody spinal fluid was removed. There were 52 cells per c.mm., of which 10 were polymorphonuclears and 42 lymphocytes. A right subtemporal decompression was done on the 4th hospital day. On the following day, the patient's condition was poor and her blood pressure was 144/94. Three days later she became stuporous and remained so until she expired. Her blood pressure fell steadily until it reached 102/76 on the last day.

peduncles, cerebellum, pons, medulla and cerebrum. Some nodules were confluent, others small and containing a central area of softening. A preparation from the cerebral cortex showed large islands and cords of various sized and shaped cells, with nuclei that varied greatly in staining reaction. The latter were of a bizarre appearance, being ovoid or stellar and either peripherally or centrally placed. The nuclei contained a loosely arranged chromatin network and well-formed nucleoli. These islands of tumor

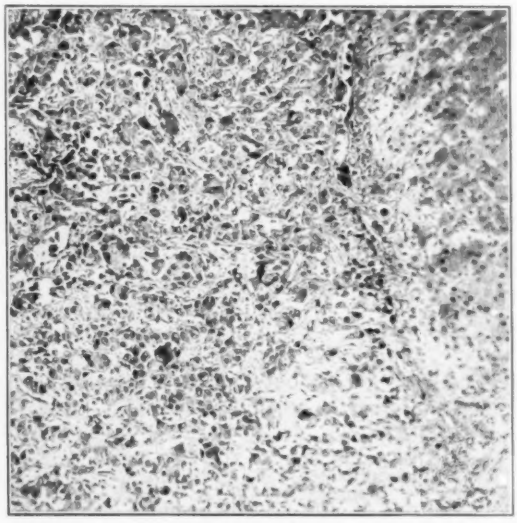

FIG. 1.—Case 1. Photomicrograph of tumor in adrenal gland. Note adrenal tissue on right side. (H. and E. × 100.)

Laboratory Data. Spinal fluid protein was 154 mg. %; the globulin was 1+. The blood sugar, blood urea and urine examinations were not remarkable. The hemoglobin and red cell count normal; white blood cells, 18,900 (69% polymorphonuclear leukocytes, 26% lymphocytes and 5% monocytes).

Morbid Anatomy. (N39–210.) The *heart* (330 gm.) showed left ventricular hypertrophy and myofibrosis. The *lungs* showed local pneumonia, edema and an infarct in the right lung base. In 1 of the main branches of the pulmonary artery was a blood clot firmly attached to the vessel wall.

Brain (1385 gm.). The cut surfaces of the cortex and medulla contained homogeneous yellow and gray, well-circumscribed nodules, some of which were mottled with red. These were present in the cerebral tissue were separated by distended endothelial lined spaces and homogeneous pink staining granular material. The perivascular spaces in these regions were increased in size and number and contained accumulations of round cells. Preparations from the pons, cerebellum and medulla showed a similar picture.

The right *adrenal* measured 5 by 4 by 0.9 cm. and weighed 7 gm. The cortex and medulla were well demarcated. The left *adrenal* measured 7 by 3 by 1.2 cm. and was grossly similar to the right. Microscopically, the adrenal glands were not remarkable except for the small nodules present in the medullæ of both glands. These showed identical histologic pictures. The cells were large, irregular, polyhedral, of a bizarre appearance, varying in size, and staining reac-

tion of the nuclei. The nuclei were vesicular, round, ovoid, triangular or stellate, and contained well-formed nucleoli. The cytoplasm was abundant and finely granular. Scattered in the vicinity of the tumor cells were collections of round cells and a few isolated plasma cells. The medullary layer was scanty and fairly well demarcated from the cortex which was compressed in the area around the nodule. The blood-vessels were distended and thick-walled and the capillaries were markedly engorged. Preparations stained with chromic salts showed a clear affinity of the stain for the tumor cells.

FIG. 2.—Case 1. Photomicrograph of metastasis in the brain. (H. and E. × 100)

TABLE 1.—BLOOD PRESSURE DURING HOSPITAL STAY (CASE 1)

Admission	2nd day	3rd day	4 h day (decompression done)	5th day	6th day	7th day	8th day	9th day	10th day
160/100	140/90 146/94	150/96 178/90	160/110	182/104	152/70 130/68	140/80 134/80	130/76 140/80	116/80	102/76

Anatomic Diagnosis. Pheochromocytoma in adrenal glands with metastases in brain; wound of recent subtemporal decompression (right); pneumonia, focal, bilateral; edema of lungs; petechiosis of pleura (right); thrombosis in branch of pulmonary artery (right); infarct in lung (right); dilatation of heart; myofibrosis cordis; congestion of viscera; arteriosclerosis, generalized.

The above case is the ninth record of malignant bilateral adrenal pheochromocytoma and it is the only reported case with metastases to the brain. Practically all previously reported cases of malignant lesions had a normal blood pressure.[5,11,15,20] In this case (see Table 1) the blood pressure readings were somewhat elevated during the patient's hospital stay. However, the high readings may be explained by increased intracranial pressure (330 mm. of water on spinal tap) with accompanying hypertension and slow pulse. From the table below it will be seen that the blood pressure began to drop shortly after decompression was performed and continued to drop until the death of the

patient. Thus, this case is very similar to the other reported cases of malignant pheochromocytoma except for the location of metastases. It may be well to point out that, as in the previously reported cases,[18] the tumor was present in both adrenal glands.

The general absence of hypertension in the malignant pheochromocytoma has not been explained. It is probable that many of the malignant cells do not have the property of secreting the pressor substance as do the cells of the benign tumor. It would be interesting to try to demonstrate this pressor substance in the blood of a patient with malignant pheochromocytoma as was done by Beer *et al.*,[1] in a case with a benign lesion. This unfortunately was not done.

Histologically the structure of the malignant tumor was similar to that of the benign lesion, so that cellular structure alone cannot be used as a reliable criterion of malignancy in this type of tumor. We are in agreement with other authors that the only indication of malignancy is the presence of metastases.

The second case in our series is the forty-ninth reported case[4,8] of benign pheochromocytoma proven by cessation of symptoms after operation. This case is being reported in greater detail in another publication. It demonstrates a fairly typical clinical history.

Case 2. B. S., 34 year old white female, about 11 months before admission, had occasional severe generalized headaches, vomiting and irritability. She was comparatively well after that until just before the termination of her pregnancy (1 month before admission), when she again developed headaches and some dizziness. During this last pregnancy, blood pressure, urine and blood chemistries were within normal limits. The day after delivery (2 weeks before admission) the patient developed severe headache, retching, vomiting and dizzy spells brought on by alteration in posture. These symptoms persisted. The neurologic examination, 1 week before admission, was negative. The patient became more drowsy, and 3 days later a neurologist noted restlessness followed by left hemiparesis.

Physical Examination. The patient was semicomatose and somewhat disoriented. She ignored the existence of the left side of her body and exhibited the right hand and leg when asked to show her left. Her eyes deviated to the right and were unable to move to the left of the midline. There was slight blurring of the optic disk margins and left hemianopsia. Sensation on the left side of the body was diminished. The Babinskis were positive bilaterally and the deep reflexes were hyperactive on the left side. The urine examinations, blood counts, blood chemistries and serology were not unusual. Lumbar puncture showed an initial pressure of 300 mm. of water, and a final pressure of 170 mm. of water. The fluid was clear and no cells were seen. The spinal fluid protein was 50 mg. %, with a trace of globulin.

Course. Within the next few days the patient became better oriented; her memory improved and she demonstrated her left hand by picking it up with her right. The ventriculogram was negative. The patient continued to have bouts of nausea, but her mental status improved and the left hemiparesis was less marked. Eye examination revealed well-outlined optic disks, with some hemorrhage into the left disk. Visual fields revealed left homonymous hemianopsia. The patient left the hospital with residual hemiparesis, spacial disorientation and occasional nausea. Blood pressures, taken twice daily during her hospital stay, varied from 84/60 to 166/124. Most values were around 110/65.

Second admission (1 year later): A month after her last admission the patient was having attacks of nausea, with blood pressure up to 260/180. The urine examination at this time revealed 2+ albumin and casts. Since then, her blood pressure varied greatly from 90/40 to 280/190, and the transition from low to high blood pressure was observed within 5 minutes. Two months before the second admission, the patient's vomiting recurred and was accompanied by severe frontal headaches. The blood pressure was 190/150 during 1 attack. These attacks continued until admission.

Physical Examination. The blood pressure was 178/110 and the pulse 108 per minute. There was increased muscle tone on the left side of the body with "claw hand"

on the left. The motor power of the upper and lower extremities on the left was diminished. There were hyperactive tendon and superficial reflexes on the left side. The laboratory work and Roentgen rays of the chest were negative. The glucose tolerance test showed a normal curve.

pressure during the last episode was 190/140. A spinal tap showed a normal pressure. Cell count, chemistry and serology were normal. The patient remained unresponsive until the next day. A neurologic consultant saw the patient several days later and she had only the residual left hemiparesis. It was

FIG. 3.—Case 2. Photograph of gross tumor.

Course. The patient had a left-sided clonic convulsion, lasting 45 seconds, followed by profuse perspiration. The blood pressure at this time varied from 100/80 to 240/180 within 3 minutes, with a pulse of 110 to 120. Intravenous pyelogram and retrograde pyelogram showed the right pelvis and calyces somewhat deformed. The kidney outline was normal. Perirenal insufflation was done, but the patient became markedly cyanotic and nauseated, with a very rapid pulse after 230 cc. of air was injected. The examination was discontinued and the patient recovered quickly. About 2 hours later the patient had a clonic seizure lasting about 40 seconds, involving the right arm and leg. The eyes were deviated to the left, the jaws were clenched and the patient was "foaming at the mouth." Five minutes after the seizure, she was lying relaxed with her eyes closed. The right Babinski was positive and the blood pressure was 106/84 at that time. There were similar episodes $\frac{1}{2}$, $\frac{3}{4}$ and $2\frac{1}{2}$ hours later. The blood thought that the episodes mentioned above could be explained on the basis of vascular spasm, possibly reflexly stimulated by perirenal air insufflation. The clinical impression was pheochromocytoma, and at operation a globular cystic tumor was removed from the right adrenal area. Her postoperative course was uneventful and she was discharged $2\frac{1}{2}$ weeks later.

The patient returned to the hospital subsequently over a period of 3 years because of "claw hand" and contracture of the foot both on the left side. The blood pressure, 1 year after operation was usually about 120/90; 3 years after operation it was 110/70. There were no attacks of any kind since operation. The patient's blood pressure during her 2nd hospital day varied from 94/78 to 220/150 except for 2 days postoperatively, when the blood pressure hovered around 78/50.

Surgical Pathology. (S.P. 43–889.) The tumor removed at operation was a cystic mass measuring 1.05 by 10 by 4.5 cm. and

weighing 310 gm. The external surface in some areas was smooth and glistening, and in other areas it was covered by adipose and fibrous tissue tags. At one end of the specimen was attenuated adrenal glandular tissue. On section, the cyst contained clotted blood and friable soft, pale brown tissue. The inner surface of the cyst was yellow and smooth and measured up to 2 cm. in thickness. Between the outer and inner surfaces was soft pale pink and brown tissue. In the region of the adrenal remnant, section revealed a narrow rim of ochre-colored cortex, with a pale brown medullary zone, which was poorly demarcated from the underlying tumor tissue. In 1 preparation, bordered by a capsule of hyalinized fibrous connective tissue, there was a fairly broad zone of adrenal cortex, in which the different cortical zones were well demarcated. In many cells, the cytoplasm was vacuolated, while in others it was clear and acidophilic. The medulla was replaced by tumor tissue, which showed a variegated picture. In some areas the cells were in an alveolar arrangement and were, for the most part, small,

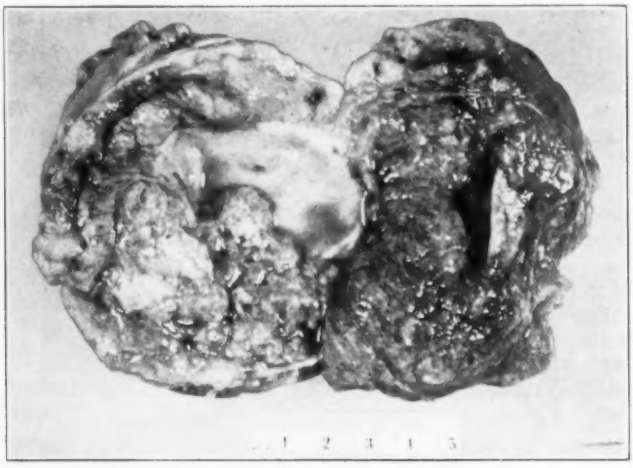

FIG. 4.—Case 2. Photograph of cut sections of tumor.

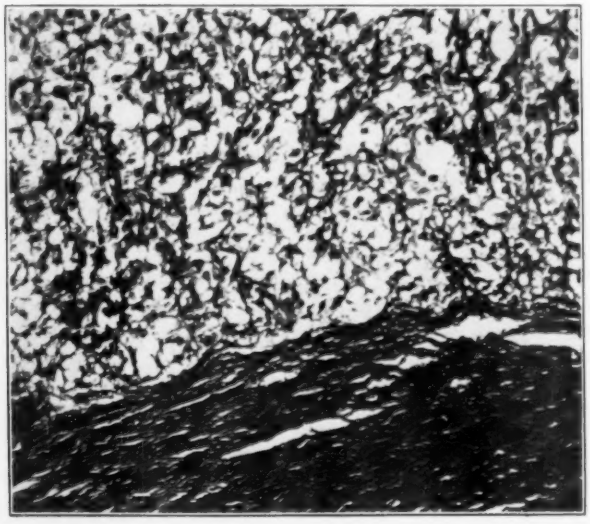

FIG. 5.—Case 2. Photomicrograph of tumor. Note the dense capsule. (B. and E. × 100.)

with deeply staining round nuclei, acidophilic cytoplasm and distinct cell borders. In other areas the cells varied more widely in size and shape; most of them were irregularly polygonal with granular or clear cytoplasm, distinct cell outlines and round or oval vesicular nuclei. Some cells contained more than 1 nucleus. The stroma was scanty and vascular. With the chromaffin stain the nuclei were blue and the cytoplasm stained a yellow green. Separating the lobules in places were broad bands of connective tissue. Other preparations showed a similar picture. This was diagnosed as a pheochromocytoma of the right adrenal gland.

The neurologic signs and symptoms which were present at the first admission were probably due to a cerebral hemorrhage resulting from the hypertension. The ensuing hemiparesis improved, but contractures of the left hand and foot remained. However, over a period of 3 years after removal of the tumor, the patient's blood pressure has remained within normal limits. There has been no evidence of new lesions in the fundi, kidneys or brain, which one might have expected if the hypertension had remained. This patient is now comparatively well despite a major cerebral vascular accident over 3 years ago.

The convulsions which occurred during the patient's 2nd hospital stay were either the result of cerebral vascular spasm or were rapidly successive paroxysms of hypertension, more likely the latter.

The diagnosis in this case was much easier clinically than in Case 3, because of the more or less typical paroxysms which were present here.

In view of Smithwick's finding that 0.5% of 1000 hypertensive patients had pheochromocytomata (cited by Goldenberg *et al.*[7]), the diagnosis of this lesion has increased importance. Furthermore, it is likely that the incidence of this lesion is even higher, since Smithwick probably did not explore the remainder of the chromaffin system in these patients and these tumors may occur anywhere in this system.

Case 3. A. D., a 55 year old white male, was admitted with a history of vomiting, disorientation and collapse of 30 hours duration. About 30 hours before admission, the patient was found lying on the floor in a pool of vomitus. He was confused, restless and disorientated. He was admitted to another hospital where a spinal tap was done. The specimen, later sent to this hospital, was grossly bloody. The morning of admission the patient was still vomiting occasionally and complaining of slight headache and stiff neck. He became less confused and less restless shortly after admission. The patient had a hypertension of over "200" for several years. There were no previous similar episodes. He had moderate exertional dyspnea for 2 years and glaucoma for many years.

Physical Examination. The patient was a well-developed and well-nourished, confused, restless, white 55 year old male with slurred speech. His neck was stiff and the pupils were pin-point. There was increased intraocular tension bilaterally. The left cardiac border was about 1 cm. to the left of the midclavicular line. The clinical impression was subarachnoid hemorrhage; hypertensive cardiovascular disease with mild decompensation and chronic glaucoma.

Course. The patient's blood pressure and temperature rose steadily during the 5 days of his hospital stay. On the day following admission he was stuporous and spinal fluid was bloody with increased pressure. Two days later there were general hyperreflexia and marked rigidity of the neck. He complained constantly of headache and dizziness. The initial spinal fluid pressure at that time was 320 mm. of water; the final pressure was 130 mm. of water. The fluid was bloody. The patient expired the next day.

Laboratory Data. The only relevant data includes a white blood count of 19,000 (80% polymorphonuclears, 14% lymphocytes, 5% monocytes and 1% eosinophils).

Morbid Anatomy. (N38–115.) Pupils were unequal. There was a generalized arteriosclerosis. The *heart* (570 gm.) showed hypertrophy and dilatation with myofibrosis. The *lungs* showed hemorrhages in the pleura, emphysema and pneumoliths. In the cardia of the *stomach* there was a shallow ulcer 3 cm. in diameter. The *brain* (1500 gm.) gave no gross evidence of hemorrhage. In a preparation from the right temporal lobe the meninges were infiltrated with extrava-

sated blood. Numerous large mononuclear cells were seen loaded with brown pigment. A small amount of blood was present in the fourth ventricle. In a preparation including the inferior longitudinal fissure, the latter was filled with blood and brown pigment. Large numbers of polymorphonuclears were seen in places, and blood was seen in the adjacent cortical tissue. The aqueduct of Sylvius contained small clumps of bacteria, old blood and large mononuclear cells laden with brown pigment.

The right *adrenal* gland measured 6 by 3 by 1 cm. and weighed 8 gm. In the cut surfaces the cortex and medulla were well demarcated and the latter was abundant. In the middle of the superior portion there was a large soft nodule 1 cm. in diameter, the cut surfaces of which were composed of a dark red center with a pink narrow rim. The left *adrenal* gland (6.5 by 2.5 by 1.5 cm.; weight, 9 gm.) showed cortex and medulla well demarcated. Microscopically, the left adrenal gland was not unusual. In a preparation from the red nodule seen grossly in the right gland, the medullary tissue was abundant. Within the medulla, in a large rounded area, were sheets and groups of irregular cells which resembled epithelium arranged in irregular fashion. The cell boundaries were indistinct. The cytoplasm was abundant and homogeneously pink and the nuclei were large and round or oval. Most of them were vesicular and contained large dark nucleoli. Numerous cells attained a giant size and contained 1 or more bizarre shaped nuclei which varied considerably in chromatin content. Some of the nuclei contained large pale vacuoles. Mitotic figures were fairly numerous. Many capillaries and delicate connective tissue strands separated the cell groups. The tumor tissue blended into the rim of medullary tissue which partially surrounded it. The cortical cell layers were compressed in many places.

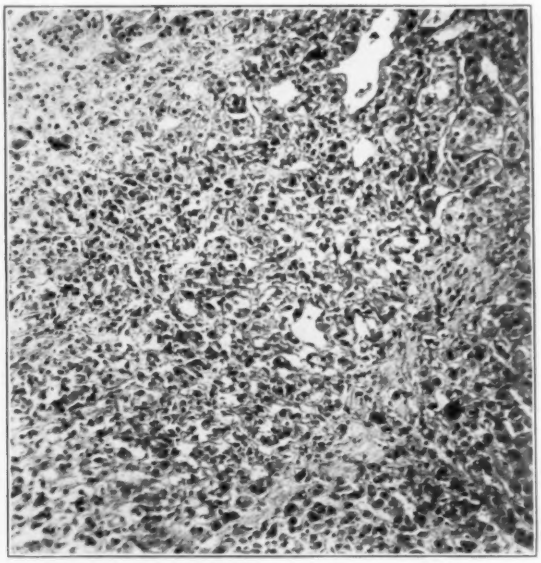

FIG. 6.—Case 3. Photomicrograph of tumor in adrenal gland. Note adrenal gland in lower right corner. (H. and E. × 100.)

Anatomic Diagnosis. Arteriosclerosis, generalized; hemorrhages, cerebral and pontine; hemorrhages in pleura with hemothorax (left); old and recent pericardial hemorrhages with hemopericardium; hypertrophy and dilatation of heart; myofibrosis cordis; passive congestion of viscera; pheochromocytoma of right suprarenal gland.

The pheochromocytoma in this case was unsuspected until autopsy. However, this patient had a long history of sustained

hypertension with a systolic blood pressure of over "200." It is true that there is no history of paroxysmal hypertension or any symptomatic paroxysms which may be associated with hypertension in these cases. Nevertheless, it is probable that the hypertension and the associated changes in this case was due to the pheochromocytoma. Similar cases were reported by Green[9] and Thorn.[19]

The life of the patient in this case might have been saved had the diagnosis been made before his cerebral hemorrhage. The possibility of pheochromocytoma must be kept in mind in studying any case with hypertension, whether it be labile or continuous. There are 2 tests which have been used as diagnostic procedures which seem relatively simple and which do not carry the danger of perirenal air insufflation. These are the histamine test of Roth and Kvale[17] and the more recent use of benzodioxane by Goldenberg *et al.*[7] These tests should prove useful when the diagnosis of pheochromocytoma is suspected.

Case 4. E. M., a 40 year old white male, was admitted complaining of pain in the throat, blood-streaked vomitus and abdominal pain. He swallowed 23 gm. of bichloride of mercury about ½ hour before admission. There was no past history of hypertension or any other illness.

Physical Examination. The patient was acutely ill, with cyanotic face, lips and ears. The abdomen was moderately distended and diffuse tenderness was present. The blood pressure was not recorded on admission.

Course. On the 3rd hospital day his condition was poor. He was vomiting, had headaches and hiccoughs. His blood pressure was 148/90. On the 6th and 7th hospital days he had tarry stools and coffee-ground vomitus, and voided only 180 cc. of urine. It was noted that his blood pressure was falling, but the actual values were not noted. On the 9th hospital day he had generalized convulsions and complete anuria and died on the next day.

Laboratory Data. The blood urea nitrogen rose from 17.9 to 83.3 mg. per 100 cc., the blood creatinine from 1.8 to 10 mg. per 100 cc., the uric acid from 7.6 to 8.2 mg. per 100 cc. Six urine examinations showed a heavy trace of 4+ albumin. They were loaded with casts and white blood cells. The red blood count was 5.35 million, with 95% hemoglobin. The white blood count was 17,800 (87% polymorphonuclears, 10% lymphocytes, 2% monocytes, 1% eosinophils).

Morbid Anatomy. (N 1041.) The *heart* weighed 480 gm. The myocardium of the left ventricle was hypertrophied and the right chambers were dilated. The *pulmonary alveoli* were filled with fluid and many hemorrhagic areas were seen scattered throughout the lungs. Marked congestion was present. The *liver* weighed 1820 gm. Cloudy swelling and granular degeneration were present. The esophageal mucosa was deep red. There were linear gray escharotic lesions extending to the *stomach*. The mucosa was denuded in many areas. There was marked congestion, hemorrhage and round cell infiltration. The stomach showed many hemorrhagic areas. The *small intestine*, *cecum* and *sigmoid* showed extensive hemorrhagic lesions of the mucosa. A few pin-point hemorrhages were seen in both *kidney* cortices. On section, the cortex was pale and edematous. The pelves showed many hemorrhagic areas. Many of the kidney tubules showed desquamation of the lining cells and their lumina were filled with granular material. The brain showed congestion and edema and weighed 1210 gm.

In the right *adrenal* gland medulla there was a gray nodule about 1 cm. in diameter. This nodule was surrounded by compressed cortical tissue which varied in thickness, with connective tissue outside of it. In one area the capsule was fragmented and absent. In another area the medullary tissue reached the connective tissue capsule. Within the medullary tissue, the cytoplasm stained blue and appeared granular. In many areas the cell outlines were indistinct and most of the cells were stellate in shape. The nuclei were round and oval and vesicular. Distinct nucleoli were seen in most nuclei. Occasional mitotic figures were seen. The cells were arranged in small groups separated by delicate connective tissue. There were many blood-vessels distended with red blood cells.

Anatomic Diagnosis. Mercurial nephrosis; ulceration and hemorrhage in gastro-intestinal tract; parenchymatous hepatitis; pheochromocytoma of right adrenal gland.

CASE 5. J. F., a 61 year old white male, was first seen at this hospital 8 years before admission with epigastric pain, constipation, loss of weight and pallor. At this admission, he had Roentgen ray evidence of a duodenal ulcer. His blood pressure at that time was 90/70. During the 4 years before admission the patient had 4 normal electrocardiograms, 2 normal chest Roentgen rays, and his blood pressure on 5 occasions varied from 126/76 to 150/90. His chief complaints on admission were weakness and loss of about 100 pounds in 6 months. He also had pain in the epigastrium and in the right upper quadrant. This pain was not related to food or respiration. He had severe anorexia at the same time.

Physical Examination. On admission the patient's temperature was 102.6° F. pulse 110 per minute, and the blood pressure 118/70. He was a well-developed, poorly nourished, elderly white male showing pallor and loss of weight. There was pain and tenderness in the epigastrium and in the right upper quadrant. The liver was palpable 2 finger breadths below the right costal margin, and there was some fullness at the right side of the epigastrium.

Course. At operation on the 5th hospital day, subhepatic and subphrenic abscesses were seen and drained. On the 19th hospital day, the patient's wound was draining profuse purulent material. He became drowsy and disoriented and there was evidence of thrombophlebitis of the left leg. On the 29th day, he had chills and fever and it was noted that his general condition was poor. Thrombophlebitis was still present. On the 34th day, the patient did not void at all. He had a high fever, continued to go downhill, and died 4 days later.

Laboratory Data. Eight urine specimens were not remarkable. The hemoglobin varied from 50 to 67%. The red blood count varied from 2.6 to 3.3 million cells. The white blood count varied from 13,000 to 26,000. The polymorphonuclears varied from 77 to 93%; the lymphocytes from 5 to 20%. The sedimentation rate was always between 125 and 137 mm. per hour. The

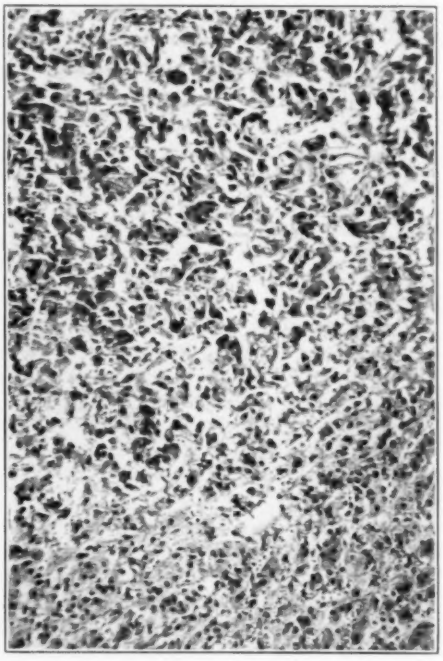

FIG. 7.—Case 5. Photomicrograph of tumor in the adrenal gland. Note normal tissue at bottom. (H. and E. × 100.)

icterus index was 14.7 and 16. The blood sugar, urea, protein and A/G ratio were not remarkable. The patient's blood pressure during his hospital stay varied from 110/50 to 130/80.

Morbid Anatomy. (N43–137.) The *skin* was lemon yellow, and the sclerae icteric. There was a sinus tract opening at the upper part of the abdominal wound. Many adhesions were found in the abdomen and a large amount of creamy green yellow odorless pus was also seen. The *heart* showed some fatty infiltration. The *lungs* showed abscesses and fibrosis. The esophagus revealed chronic inflammation and there were ulcers in the duodenum, 1 of which perforated and showed a communication with the inferior surface of the liver. Between the liver and the adherent diaphragm t ere was a moderate amount of creamy yellow green pus and a large collection of pus within the caudate lobe of the liver. There were abscesses and an infarct in the right lobe of the *liver*. The *kidneys* showed nephrosclerosis. There was a large organized thrombus in the left internal saphenous vein. *B. coli* and *Staph. aureus* were obtained on culture from these abscesses. The prostate also showed several small abscesses.

The right adrenal gland measured 6 by 3.4 by 0.8 cm. and weighed 6 gm. The left gland measured 6.2 by 3.5 by 1.1 cm. and weighed 8 gm. The external surfaces were discolored gray green. On section, the cortex and medulla were distinct. The left adrenal was the seat of a small circular nodule which on cross-section was pink in color and measured 0.8 cm. in diameter. Microscopically, both adrenal glands were not remarkable except for the small tumor mass arising from the medulla of the left adrenal gland. This nodule was almost entirely surrounded by compressed cortical tissue. In 1 area the nodule was seen to merge with normal medullary tissue. Within this mass the cells were arranged in small groups, separated by delicate vascular connective tissue. The cytoplasm of the tumor cells was granular and stained light blue. The nuclei stained dark blue and varied greatly in size. Most of them were round and oval and vesicular. Nucleoli were seen in many nuclei.

Anatomic Diagnosis. Ulcers in duodenum with perforation; perihepatic and intrahepatic abscesses, wound of operation for; pylephlebitis; infarct in liver; icterus; abscesses in lungs with fibrosis; thrombophlebitis, external iliac, femoral and saphenous veins, left; anemia; congestion of viscera; arteriosclerosis, generalized; fatty infiltration in heart; esophagitis, chronic; nephrosclerosis; pheochromocytoma in adrenal gland, left; prostatitis, chronic with abscess.

TABLE 2.—BLOOD PRESSURE DURING HOSPITAL STAY (CASE 3)

Admission	2nd day	3rd day	4th day
184/86	192/90	220/90	226/90 220/102 220/104

Cases 4 and 5 never had hypertension, paroxysmal or sustained, so that the pheochromocytoma had no obvious clinical effect in these 2 cases. These 2 patients died of causes unrelated to their pheochromocytomata. Lazarus and Eisenberg[13] stated, "Paragangliomata are usually small and symptomless, as a result of which most of them have been found at autopsy." Moreover, the age of these 2 patients (40 and 61) was such that it cannot be said that they were in the early stage of the disease and that they would have developed symptoms if they had gone on long enough. This is particularly true in view of Case 2, of pheochromocytoma with a more or less typical story in a woman 34 years old. Thus, there is no indication that the symptomless lesions are earlier stages of the symptomatic ones.

Summary and Conclusions. A series of 5 cases of adrenal pheochromocytoma is presented as examples of the various clinical types of this tumor. They include (1) the malignant tumor with metastases, as in Case 1; (2) the benign tumor with

hypertension (paroxysmal) in Case 2 and sustained in Case 3; (3) the benign tumor with no signs or symptoms, found accidently at autopsy, as in Cases 4 and 5.

The malignant variety is exceedingly rare. The case in this series is the ninth on record and the only one with metastases to the brain. Antemortem diagnosis and treatment of the malignant lesions give little promise of improvement, since the earliest signs are usually those of metastatic involvement. Moreover, the presence of metastases is the only reliable criterion of malignancy in these cases, since the histologic structure of the benign and malignant tumors is similar. The absence of hypertension in the patients with malignant lesions is unexplained. Perhaps the malignant cells lose the property of secreting the "pressor substance." We noted that the affinity of the primary and metastatic lesions for chrome salts was just as great as in the benign tumors.

The benign pheochromocytoma with paroxysmal hypertension is well recognized today. However, in the group with sustained hypertension, great room for improvement in diagnosis exists. In these latter cases the diagnosis must always be kept in mind and definite effort made to rule it in or out. The use of the Roth-Kvale[17] histamine test or the benzodioxane test of Goldenberg *et al.*[7] may be important in this respect.

The benign pheochromocytomas without clinical signs and symptoms have little or no diagnostic significance at present. However, the presence of hypertension in some patients with benign tumors and its absence in others with the same lesion is unexplained. There is some indication that these symptomless lesions are not precursors of the symptomatic ones from the comparative ages of these patients. Moreover, the size of the tumor in Case 3 with sustained hypertension was approximately the same as in Cases 4 and 5 without hypertension, so that the presence of symptoms does not seem to depend on the size of the lesion.

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AMYLOIDOSIS IN RHEUMATOID ARTHRITIS
A Report of Ten Cases

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On the basis of previous reports in the literature amyloidosis complicating rheumatoid arthritis is uncommon, and to date has been reported only 40 times, but there is reason to believe that the 2 conditions coëxist more frequently. The fact that simultaneous occurrence was usually discovered at postmortem examination indicates a general lack of awareness of the association. Four additional postmortem and 6 living cases of amyloidosis occurring in patients with rheumatoid arthritis are now reported.

Trasoff, Schneeberg and Scarf[9] completely reviewed the literature up to 1943 and again focussed attention on the association of the 2 diseases. Since then 8 additional cases have been reported.[3,4,7,9,11] Review of the additional cases adds little to the conclusions reached by Trasoff, Schneeberg and Scarf.

Postmortem Cases. The records of 58 patients with rheumatoid arthritis who came to postmortem study were reviewed to determine the incidence of amyloidosis. There were 4 cases in which amyloidosis could not be attributed to causes other than rheumatoid arthritis.

The arthritis in the group studied was severe. The duration varied from 11 to 23 years (Table 1). There was no obvious difference in duration or severity from the non-amyloid group. Despite the presence of suggestive clinical evidence of amyloidosis, the Congo red test had not been performed in any of these cases, since the diagnosis was not suspected antemortem. Edema was present in 3 of the 4 cases, hepatosplenomegaly in 1 and hypo-albuminemia in all 3 cases in which the serum proteins were estimated. Unfortunately, hepatic and renal functions were not well studied in this group. The urine in all instances showed albumin, varying from a trace to 4+. None of the patients died in uremia, though the non-protein nitrogen was elevated in 1 and the blood urea nitrogen in another case.

The postmortem findings showed amyloidosis of varying severity and distribution, involving liver, spleen and kidney in every case, and, in addition, in 1 case the adrenals, pancreas and heart. Case 2 had a metastatic chorioepithelioma complicating the rheumatoid arthritis. The rapidity of the downhill course following the appearance of the tumor made it unlikely that the amyloidosis was in any way related to the occurrence of the tumor. The presence of rheumatic heart disease in 3 of the 4 cases is of interest.[8] Amyloidosis was not the immediate cause of death in any of the cases.

Living Cases. With these results in

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TABLE 1.—POSTMORTEM CASES OF RHEUMATOID ARTHRITIS AND AMYLOIDOSIS

Pertinent Clinical and Laboratory Findings

	Case 1. A. E. 52 yrs. Male	Case 2. J. S. 34 yrs. Male	Case 3. P. W. 53 yrs. Female	Case 4. R. M. 33 yrs. Male
Pathologic diagnosis	Rheumatoid arthritis; chronic rheumatic valvulitis; amyloidosis, liver, spleen, kidney	Rheumatoid arthritis; chronic rheumatic valvulitis; fibrous pericarditis; chorionepithelioma with metastases; amyloidosis, liver spleen, kidney; acute pyelonephritis	Rheumatoid arthritis; pulmonary fibrosis; necrotizing bronchiolitis, acute; chronic adhesive pericarditis; amyloidosis, liver, spleen, kidneys, adrenals, heart, pancreas	Rheumatoid arthritis; rheumatic heart disease, inactive; amyloidosis, liver, kidneys.
Duration of arthritis (yrs.)	18	8	23	11
Physical examination:				
Blood pressure	140/80	144/98	120/80	110/70
Edema	2+	2+	1+	0
Spleen	0	+	0	0
Liver	0	+	0	0
Kidney function:				
Specific gravity	1 012	1 018	1 012	1 020
Albumin	2+	2+	4+	Trace
Microscopic	Many hyaline casts	Many RBC, WBC, casts	Occasional casts	Neg.
BUN (mg. per 100 cc.)	17	NPN 75	26 8	15 6
Liver function:				
Albumin/globulin (gm. %)	3.6/2.6	3.0/2.7	2.5/5.1	–
Cholesterol T/E (mg. %)	–	162/98	–	–
BSP % (30 min.)	–	None	–	None
Hematology:				
Red blood count	3 8	2 8	3 2	4 0
Hemoglobin (%)	60	44	69	80
White blood count	15,200	18,600	–	–
ESR (mm./hr.)	88–112	35–85	85 96	50/90
Strep.—hemagglutinins	Neg.	Neg.	–	Neg.
Antistreptolysin	200	0	–	50
Gonococcus—compl. fixa.	Neg.	Neg.	–	3+
Therapy	Typhoid vaccine Rubophen	Gold Liver extract	Gold Liver extract	Typhoid vaccine

TABLE 2.—LIVING CASES OF RHEUMATOID ARTHRITIS AND AMYLOIDOSIS

Pertinent Clinical and Laboratory Findings

	Case 1. R. S. 32 yrs. Male	Case 2. G. G. 50 yrs. Male	Case 3. J. M. 43 yrs. Male	Case 4. M. B. 39 yrs. Male	Case 5. M. W. 54 yrs. Male	Case 4. M. M 54 yrs. Male
Clinical diagnosis	Rheumatoid arthritis; rheumatic heart disease, M.I.; amyloidosis	Rheumatoid arthritis; duodenal ulcer; amyloidosis	Rheumatoid arthritis; pulmonary tuberculosis, inactive; amyloidosis	Rheumatoid arthritis; rheumatic heart disease, MI, MS, AI; amyloidosis	Rheumatoid arthritis; rheumatic heart disease, MI, MS; amyloidosis	Rheumatoid arthritis-rheumatic heart disease, MI; MS; Amyloidosis
History	Gonorrhea 11 yrs. ago, cleared	...	Pulmonary Tb. regan 11 yrs. ago Inactive for 9 yrs.	Gonorrhea 10 yrs. aao		
Duration of arthritis (yrs.)	10	12	9	29	15	3
Physical examination:						
Blood pressure	104/52	110/74	120/92	115/65–150/0	104/50	115/80
Edema	4+	2+	0	1+	2+	2+
Spleen	0	+	+	+	+	0
Liver	0	+	+	+	+	+
Kidney function:						
Specific gravity	1.019	1.023	1.018	1.017	1.029	1.019
Albumin	4+	4+	4+	0.1+	3+	2+
Microscopic	Many hyaline casts	Many hyaline casts	Many hyaline casts	Neg.	Many hyaline casts	Neg.
BUN (mg. %)	16.6	13.9	NPN 28	12.0	11.4	15.7
Urea clearance (%)	126–39.2	70	70	45	52	55
PSP % (1 hr.)	12	18	15	–	35	37
Liver function:						
Albumin/globulin	1.6/2.1	2.7/3.2	3.8/2.9	3.9/2.9	3.9/2.4	3.5/2.6
Cholesterol T/E	280/20	225/?	290/207	125/97	202/161	205/153
BSP % (30 min.)	5	5	None	3	None	None
Cephalin flocculation	Neg.	Neg.	3+	Neg.	3+	Neg.
Amino acid N (mg. per 100 cc.)	3.9	3.6	4.5	4.0	4.6	5.1
Hematology:						
Red blood count	2.6	2.8	4.3	3.7	3.5	4.4
Hemoglobin (%)	38	36	56	60	58	73
White blood count	12,800	8400	7000	6500	9400	9000
ESR (mm. per hr.)	29–74	30	60–120	34–108	20–85	22–96
Strep.—hemagglutinins	Neg.	–	–	–	–	–
Antistreptolysin	–	–	250–500	833	333	166
Plasma volume	4.920	5.293	5.293	4.100	4.180	–
% Congo red absorption	100	95	93	86	86	81
Liver biopsy	–	Amyloidosis	–	–	Amyloidosis	–
Therapy	Typhoid vaccine, gold, Roentgen ray, sulfonamides, malaria	Gold, Roentgen ray	Gold, pneumothorax	Gold, fever, Roentgen ray, sulfur, vitamin D, sodium thiosulfate	Typhoid vaccine, sulfur, gold, Roentgen ray, bismuth, liver extract, salicylates	Salicylates, vitamin C

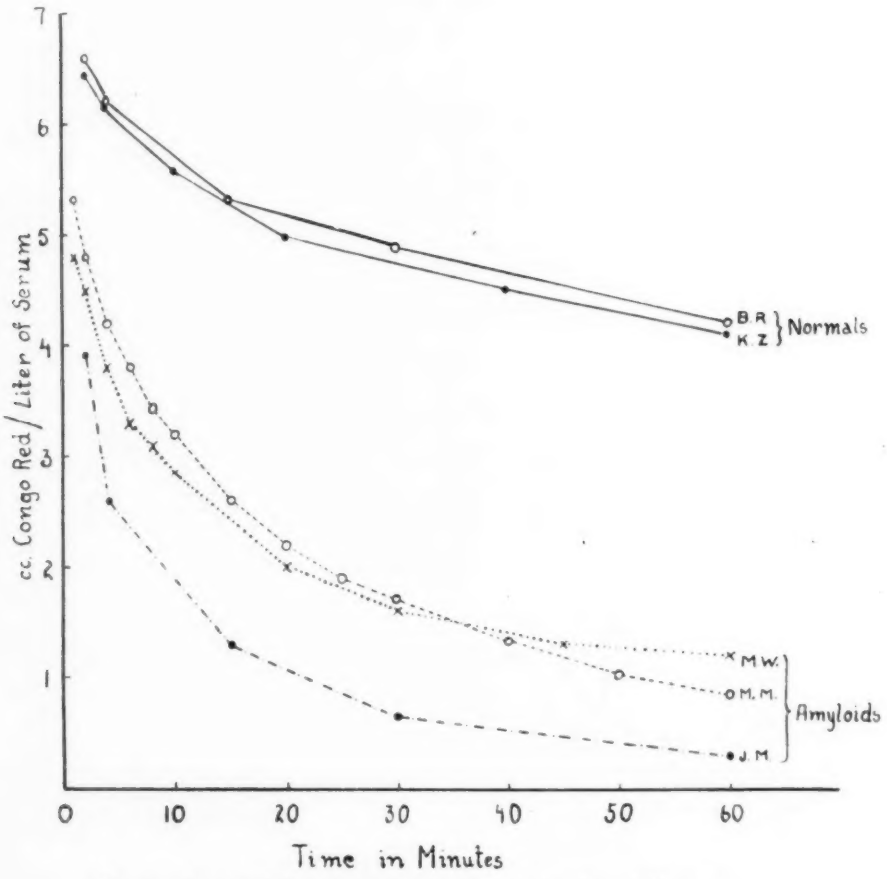

FIG. 1.—Congo red disappearance curve in normal and amyloid cases.

mind, a search for amyloidosis was made among the 56 living cases with rheumatoid arthritis. The patients were subjected to thorough study, including measurement of renal and hepatic function in all cases suspected of amyloidosis. The Congo red test as modified by Taran and Eckstein[8] from Bennhold's original method was used.[2] A Coleman junior spectrophotometer was used for the colorimetric comparison. The interpretation of the Congo red test depended as much upon the slope of the curve of disappearance as it did upon the absolute amount of dye absorbed (Fig. 1). Five of the 6 cases showed Congo red absorption ranging from 86 to 100% 1 hour after injection. In the remaining case, 81% of the injected dye was removed after 1 hour. Wherever possible, liver biopsy was performed to confirm the clinical impression.

Amyloidosis was found in 6 patients (Table 2). The duration of the arthritis in this group ranged from $2\frac{1}{2}$ to 29 years and was severe in all instances. It was no worse, on the average, than in many of the arthritics without amyloidosis of equal or longer duration. It appears certain that amyloidosis was secondary to rheumatoid arthritis in 5 of the 6 cases. The exception (Case 3) had tuberculosis that had been pronounced arrested and had remained so for 8 years. Clinical findings attributable to the amyloidosis appeared sometime after the tuberculosis had become arrested, at a time when his

rheumatoid arthritis was progressing rapidly.

Hepatosplenomegaly was present in 4 cases and hepatomegaly alone in 1. Five of the 6 patients showed peripheral edema of varying degree. Two of these 5 had serum albumin levels below 3 gm. The serum globulin was normal in all instances.

Albuminuria of varying degree was present in all of the patients. The only formed elements found in the urine were hyaline casts and white blood cells. There was some impairment of the ability to concentrate urine but nitrogen retention did not occur. Urea clearance was above 50% of normal in 5 of the 6 cases. Oddly enough, phenolsulfonephthalein excretion was markedly impaired in all patients.

Liver function was tested in all patients. The bromsulfalein test was normal in all cases. Two patients had a 3+ cephalin flocculation, 2 had hypoproteinemia with reversal of the albumin globulin ratio. The positive cephalin flocculation occurred in patients with normal serum proteins. Hypercholesteremia and hypoproteinemia were associated in 1 patient.

A finding of great interest was the definitely low serum amino acid levels in all of our living cases, varying from 3.6 to 5.1 mg. amino acid nitrogen per 100 cc. of serum (normal values 5 to 7 mg.). This might be referable, in the absence of controlled protein intake, to poor diet, poor absorption, increased loss of protein *via* the kidneys, but the possibility exists that a disturbance of protein metabolism in the liver may be the important factor.

Hematologically all cases showed moderately severe normocytic hypochromic anemia. Evidence of rheumatic cardiac involvement occurred in 4 of the 6 living cases.

Comment. As a part of a study[10] directed toward improving the accuracy of the Congo red test for diagnosis of amyloid disease, plasma volumes were studied in 5 cases, using T-1824 (Evans blue). The volumes obtained were much greater than those predicted on the basis of body surface area (Table 2). Unusually rapid disappearance of the dye from the blood stream could give these results. Since T-1824 is a vital dye, it might be fixed by amyloid tissue in a fashion similar to Congo red. By staining sections of tissue with T-1824, it was found that amyloid tissue fixed the dye to a much greater extent than normal tissue. If phenolsulfonephthalein is also picked up by amyloid tissue, it would, of course, not be useful in the study of renal function in amyloidosis. That this state of affairs may exist is suggested by the fact that the phenolsulfonephthalein excretion test was quite low in these patients and not in accord with the results of the other tests of renal function. There is also a possibility that the failure to obtain abnormal retention of bromsulfalein in the blood stream, despite the extensive replacement of hepatic cells by amyloid deposition histologically, might be referable to a similar process.

Analysis of the data fails to show any difference in the severity and therapy between patients suffering with rheumatoid arthritis who developed amyloid disease and those who did not.

It appears that deposition of amyloid does not occur as rapidly in rheumatoid arthritis as in tuberculosis or chronic suppuration. The amyloid process *per se* was apparently not responsible for death in patients with rheumatoid arthritis. Earlier recognition of amyloidosis would permit testing the efficacy of the recently recommended therapeutic regimen of desiccated whole liver powder.[5,6]

Summary and Conclusion. 1. Four cases of amyloidosis were found among 58 autopsied cases of rheumatoid arthritis.

2. Six cases of amyloidosis were found among 56 living patients with rheumatoid arthritis.

3. The incidence of amyloidosis appears to be higher in rheumatoid arthritis than is generally believed.

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ELECTROENCEPHALOGRAPHIC RECORDS IN RELATION TO BLOOD PRESSURE CHANGES IN ECLAMPSIA

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Thirty-three electroencephalographic (EEG) records were obtained before, during and after eclamptic convulsions in 9 cases. Special attention is paid in this paper to the changes in the EEG and the improvement in the clinical picture when the high blood pressure, which was associated with the toxemia, was lowered either through the use of a caudal analgesia, veratrum viride, or by allowing sufficient time to elapse for a normal drop in the blood pressure.

As the blood pressure was lowered after use of any of these methods, the convulsions ceased and the clinical picture improved markedly. The EEGs were obtained in some cases before delivery and the blood pressure was lowered artificially; however, in others the EEGs were obtained following delivery, and whenever possible follow-up EEGs were obtained for 10 days following the delivery.

An earlier report by Whitacre *et al.*[4] gave a description of 1 case in which the EEG tracings were obtained at the same time the blood pressure was lowered through the use of a caudal analgesia. The 9 cases presented here represent a continuation of this study.

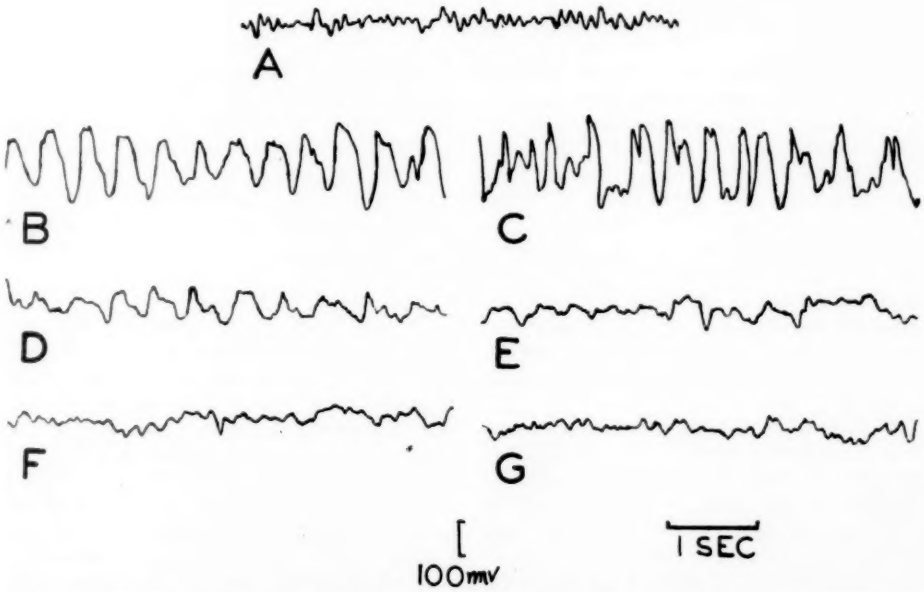

Fig. 1.—Electroencephalogram. Case 1. A, Record before delivery; blood pressure 145/100. B, Record on day following delivery. C and D, Record on same day when blood pressure was falling. E, Record on following day; blood pressure 140/120. F, Record 3 days after delivery. G, Record 6 days after delivery. (Poland Photogs.)

(*) Study facilitated by grant-in-aid from Life Insurance Medical Research Fund.

Material. Three of the 9 cases have been selected as samples for special study since a large number of tracings were obtained and because they represent the whole group of cases. Bipolar (precentral to occipital leads) were used in all sample runs reported. Summaries of the remaining cases are given following the samples.

On the following day another EEG was obtained when the blood pressure was 140/120 (Record E). A continued increase in the low voltage fast material and a decrease in the high voltage slow activity is apparent. A sample of the record obtained the following day is given in Tracing F.

The final sample (Record G) was obtained 3 days later. It should be noted in these last 3 records that there was a progressive change toward a more normal EEG. During this period of time the EEG had not completely returned to the preconvulsive level, but much improvement was shown.

TABLE 1.—CASE 1

	Date (1946)	Time	B.P.
A.	Feb. 15	....	145/100
	Feb. 17	Baby delivered (caudal analgesia)	
	Feb. 18	(2 convulsions)	
B.	Feb. 18	11:30–11:40	172/108
C.	Feb. 18	3:20	165/122
D.	Feb. 18	4:30	156/120
E.	Feb. 19	....	140/120
F.	Feb. 20	....	130/102
G.	Feb. 23	....	100/70.

CASE 1.—The EEG records obtained on this case are presented in Figure 1. This case is an example of the changes in the EEG when no specific treatment was given to lower the blood pressure at the time the EEG tracings were obtained. The routine Dieckmann treatment for eclampsia was used.

This was a Negro girl, 15 years old, who was admitted to the hospital Feb. 15, 1946, with a slightly elevated blood pressure of 145/100 and a trace of albumin in the urine. An EEG tracing was obtained at this time (see Record A). At this time the EEG was essentially normal.

On the following day the blood pressure was 170/120 and a trace of albumin was found in the urine. The next day her blood pressure was 180/120, and the baby was delivered through the use of caudal analgesia, at which time the blood pressure was dropped temporarily to 120/70.

The day following delivery the blood pressure remained elevated at 170/120, and the patient had 2 convulsions. There was 2+ albumin in the urine. At this time an EEG was obtained which showed much high voltage slow activity. Records C and D were obtained the same day when the blood pressure was coming down. At 3:20 it was 165/122, and at 4:30 it was 156/120. It may be observed here that the slow high voltage waves were giving way to the faster low voltage material.

CASE 2. A Negro girl, 19 years old. The EEG samples are presented in Figure 2. This case was selected for special study as an example of the effect of lowering blood pressure by the use of a caudal analgesia. The patient entered the hospital on Jan. 28, 1946, with a blood pressure of 170/100 and a trace of albumin in the urine. The patient had 3 convulsions before entering the hospital.

The first EEG was obtained on Feb. 9, 1946, the blood pressure ranging between 200/100 and 170/100, and the urine showed a 3+ albumin. Records A through F were obtained before and during the administration of a caudal analgesia, at which time the blood pressure was lowered from a high of 170/112 to a final stabilized level of 120/80.

Record A was obtained at 11:55 A.M. at which time the blood pressure was at its highest point. Thirty-eight cc. of metycaine was administered, and at 12:17 P.M. the blood pressure was 164/120. Much of the slow activity is still shown in the EEG (Record B).

Record C was obtained at 12:16 after an injection of 20 cc. more of metycaine

and the blood pressure had been lowered to 150/100.

Records D, E and F show the changes in the EEG as the blood pressure was lowered from 150/100 to 100/70 and stabilized at 120/80. It should be noted that as the blood pressure was lowered, more fast activity was observed and the slow waves, associated with the high blood pressure, were not found.

The baby was delivered later this same day by a low cervical Cesarean section. Records G, H and I were obtained in the 2 weeks following the delivery of the baby. Record G was obtained the day after delivery, when the blood pressure was 190/120. It should be noted here that the high slow material, characteristic of the control run 2 days earlier, predominates.

Nine days after this run, Record H was obtained, at which time the blood pressure was 158/115. Nearly all of the slow activity had disappeared and fast low voltage waves were observed. The final record (I) was obtained 3 days later, at which time the blood pressure was 154/114, and the EEG was showing a return to a relatively normal pattern.

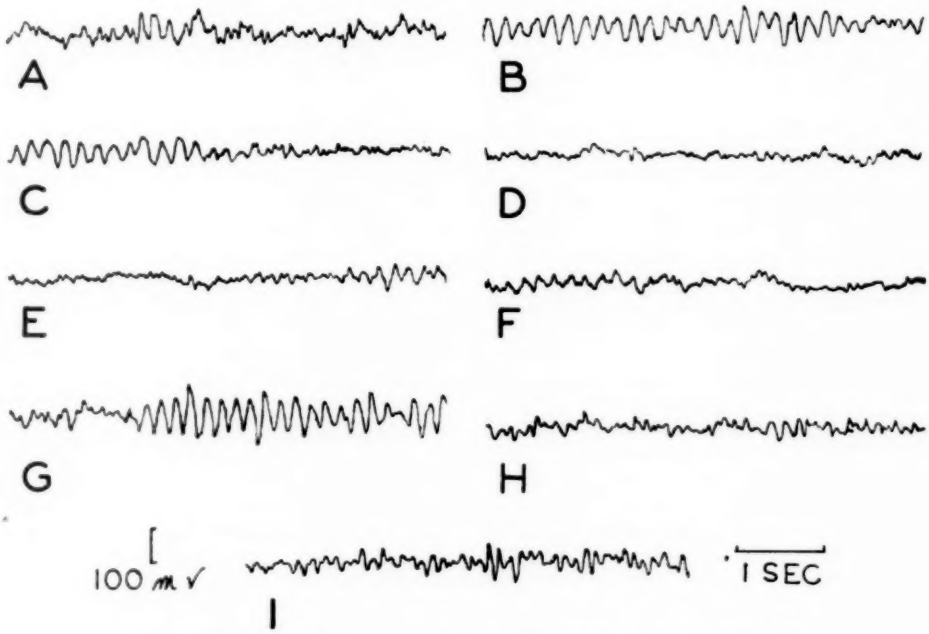

FIG. 2.—Electroencephalograms. Case 2. For details see text and Table 2.

TABLE 2—CASE 2

	Date (1946)	Time	B.P.	Caudal level
A.	Feb. 9	11:55	170/112	0
	38 cc. 1.5% metycaine hydrochloride			
B.	Feb. 9	12:07	164/120	0
	50 cc. 1.5% metycaine hydrochloride			
C.	Feb. 9	12:16	150/100	0
D.	Feb. 9	12:20	140/100	T 8
E.	Feb. 9	12:38	100/70	T 6
F.	Feb. 9	12:45	120/80	T 6
	Baby delivered Feb. 10, 1946			
G.	Feb. 11	..	190/120	0
H.	Feb. 20	..	158/115	0
I.	Feb. 23	..	154/114	0

CASE 3. A Negro girl, 21 years of age, was admitted to the hospital on June 22, 1946, with a blood pressure of 210/155, and the urine showed a 3+ albumin. This is an example of the use of veratrum viride as a method of lowering the blood pressure and the resulting changes in the EEG (Fig. 3).

The patient was brought to the EEG room while having a convulsion and the veratrum viride was used to lower the blood pressure. Record A in Figure 3 was obtained at 11:16 A.M. on this date in an interconvulsive state. The blood pressure was 200/140. At 11:20 A.M., 0.5 mg. of veratrum viride was administered.

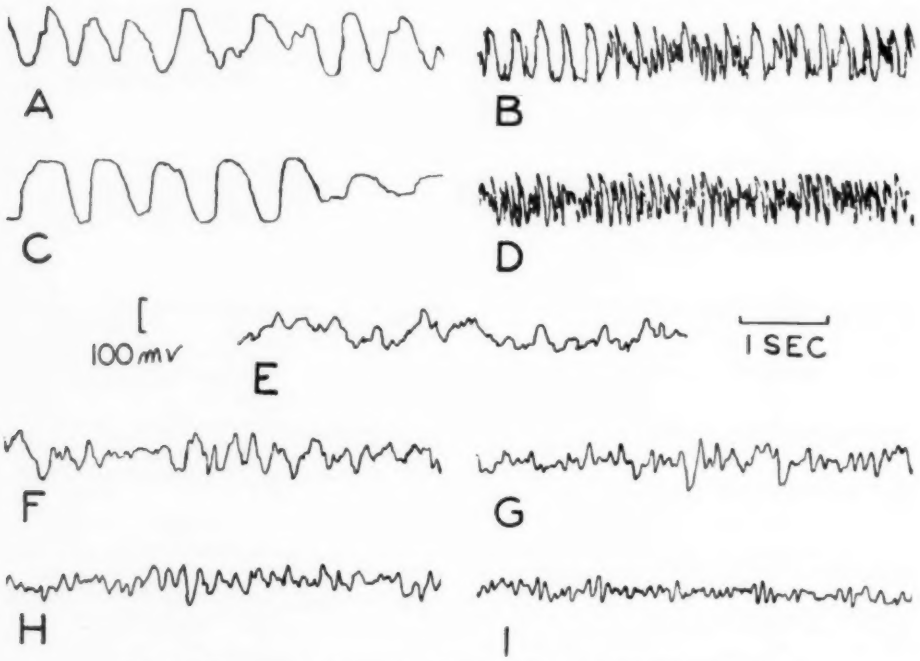

FIG. 3.—Electroencephalograms. Case 3. For details see text and Table 3.

TABLE 3—CASE 3

	Date (1946)	Time	B.P.
A.	June 22	11:16	200/140
		11:20	
		(0.5 mg. veratrum viride)	
B.	June 22	11:28	200/140
		(seizure)	
C.	June 22	11:30	205/108
		(interseizure)	
		11:32	
		(0.4 mg. veratrum viride)	
D.	June 22	11:45	160/110
		11:47	
		(0.4 mg. veratrum viride)	
E.	June 22	11:58	140/85
	Baby delivered June 24, 1946		
F.	June 26	...	140/110
G.	June 27	...	150/110
H.	June 28	...	132/110
I.	July 2	...	120/90

Record B was obtained during a convulsion at 11:28 A.M. at which time the blood pressure was still 200/140. The interseizure pattern is shown in Record C when the blood pressure was 205/108. At 11:32, 0.4 mg. more of veratum viride was administered. Record D was obtained approximately 15 minutes later during another convulsion. The blood pressure was 160/110. At 11:47 A.M. another 0.4 mg. of veratrum viride was administered and the blood pressure further lowered.

A sample of the final EEG tracing in this examination is shown in Record E at which time the blood pressure was 140/85. It should be noted here that the high voltage slow waves were suppressed and some fast low voltage activity was appearing.

The baby was delivered 2 days later, at which time a caudal analgesia was administered and the blood pressure lowered from the initial 170/120 to 100/55 for a period of 1 hour. Record F was obtained 2 days after delivery, at which time there was still a marked dysrhythmia.

Records were also obtained 3 days after delivery (G), 7 days later (H) and 9 days later (I). During this time the EEG changes were from those typical of grand mal epilepsy and the interconvulsive state, to a relatively normal pattern. The clinical picture improved similarly.

CASE 4. This patient was admitted to the hospital Feb. 7, 1946, with a blood pressure of 144/100. The baby was delivered the same day, and immediately following delivery convulsions occurred. An EEG was obtained at this time which showed complete dysrhythmia from the whole cortex, with continuous spiking localized on the right side. The patient was comatose during most of the run and had left-sided as well as generalized convulsions. The patient died a few hours later. On autopsy a hemorrhage was found involving the right internal capsule and extending into the right ventricle. All the ventricles were filled with blood but only a few patches of blood were found in the subarachnoid space. It was noted on the autopsy report that a possible cause of the death may be on the basis of toxemia in pregnancy.

CASE 5. This patient was admitted to the hospital on April 1, 1946, with a blood presure of 170/120 and a 1+ albumin in the urine. An EEG record was obtained before delivery, during which time caudal analgesia was administered and the blood pressure lowered from the initial 170/120 to 100/55 during a period of approximately 1 hour. The EEG changes were from those typical of grand mal epilepsy and the intraconvulsive state to a relatively normal pattern. The clinical picture improved similarly. Records obtained on the day following, 7 days later, and 9 days later, showed continual improvement of the EEG as well as lowering the blood pressure and alleviation of symptoms.

CASE 6. The patient was admitted to the hospital on March 21, 1946, with a blood pressure of 175/140. In this case the EEG records were obtained only at times when the blood pressure was not lowered through the use of either veratrum viride or caudal analgesia. The EEG obtained on the 1st day of admittance was dysrhythmic from all areas, showing slow and fast high voltage mixed activity. Two days later the blood pressure was 150/122 and no improvement in the EEG record was observed. Ten days later the blood pressure was still slightly elevated (140/114). The urine showed a 3+ albumin and the EEG showed a very slight improvement on the earlier runs, but was still dysrhythmic.

CASE 7. The patient was admitted to the hospital on March 13, 1946, with a blood pressure of 190/130 and a 1+ albumin in the urine. The EEG records which were obtained at this time showed gross dysrhythmia in the form of high voltage slow and fast material. Delivery was the following day. On March 14, another EEG was obtained and the blood pressure was 150/90, which showed marked improvement over the earlier run, much of the record being relatively normal.

CASE 8. This patient was admitted to the hospital on May 10, 1946, with a blood pressure of 170/110. Delivery occurred that day, and 3 days later the patient had 2 convulsions. At this time the blood pressure was 146/100 and a 3+ albumin was found in the urine. The EEG at this time showed the continuous fast high voltage activity with some mixed slow material in all leads. Another EEG was obtained 7 days later, at which time the blood pressure was still elevated (140/105) and there was a trace

of albumin in the urine. This EEG showed some improvement over the earlier run, but it was still not completely normal, showing high voltage beta waves and spiking activity.

CASE 9. The patient was admitted to the hospital on April 26, 1946, with a blood pressure of 220/145 and a 2+ albumin in the urine. An EEG was obtained at this time which showed dysrhythmia from all areas, high voltage spikes, beta and slow components. The blood pressure was lowered to 82/60 through the use of caudal analgesia and a slight improvement was observed in the EEG. Six days later the blood pressure was still elevated to 180/120 and the EEG showed little or no improvement over the earlier run and the clinical improvement was slow.

Discussion. The findings of this study may be summarized as follows: 1. Changes in the EEG were associated with a drop in blood pressure, irrespective of what caused this change in pressure. Slow high voltage activity was replaced by the more normal low voltage fast material.

2. Where the blood pressure did not change, the EEG did not improve.

3. Convulsions appeared to be controlled by the drop in blood pressure.

4. Clinical improvement was observed with drop of blood pressure and change in EEG pattern.

Indirect evidence is available which indicates that one factor which may play an important part in the changes described above is that of angiospasm or increased peripheral resistance.

Studying the pial blood-vessels in curarized cats through a window while recording brain volume simultaneously with blood pressure, Barrow, Green, Davis and Garol[1] observed dilatation of blood-vessels associated with low voltage fast EEGs after sponging the cut end of the nerve carrying parasympathetic impulses to the brain. With hyperventilation, fibrillation of blood-vessels was likewise observed, apparently concomitant with rhythmic electrical activity, and paling and constriction appeared related to high voltage activity of the brain. Such methods of observation, however, did not permit satisfactory demonstration of exact temporal correspondence.

Darrow and Graf[2] attempted to obtain more conclusive evidence on the correspondence of EEG and vasomotor activity in identical or immediately adjacent regions of the brain. In a study on cats, a cranial window was prepared. Bipolar electrodes for recording the EEG were inserted through the glass window to enable microscopic observation of the cortex near the tip of the electrodes. The window was so constructed that the glass plate containing the electrodes could be slipped around over the frame to permit contact of the electrodes with various points on the exposed cortex. The plate was held in place by a superimposed ring which exerted pressure when laterally placed conical screws were tightened. Microscopic observation of brain and blood-vessels at the point of electrode contact and the surrounding area was possible. A more objective method of study, permitting recording of observations in parallel with the recording of the EEG, was obtained by the use of a Pulfrich photometer.

In this study, electrocorticogram, EEG, and electrocardiograph recordings were made. In general, they found a tendency for increase of frequency, increased potential of fast waves, and decrease of slow activity to be associated with vasodilatation, and that vasoconstriction gave the opposite, that is, increased potential of slow waves and a decreased fast activity. These general results were found in studies with ether asphyxia, hypercapnia, atropine and pilocarpine. During the experimental work, several animals developed convulsions of the grand mal type. Spindles in the EEG were observed to be associated with waves of constriction passing along the arteries, giving them the resemblance of sausage links.

In this study the workers did not record systemic blood pressure which was obtained in the earlier study.[1] However,

it might be assumed that with the blanching of the cortex and change in the caliber of the arterioles, there was probably a rise in blood pressure due to changes in peripheral resistance.

Generalization from studies done on animals applied to those on human subjects must, of course, be cautious, because of the large number of factors which differentiate the 2 groups. There is, however, a relatively clear parallel between the findings on animal material and those obtained from the eclamptic patients in this study. It is suggested here that perhaps one of the main factors in convulsions due to eclampsia may be angiospasm. Ophthalmoscopic examinations were not made on these patients. However, this will be done in a continuation of this study.

It is apparent that a great deal more work is necessary before conclusions can be drawn as to the part played by peripheral resistance in the convulsions of eclampsia. It is suggested, however, that angiospasm may play an important rôle.

Summary. Thirty-three EEG records were obtained before, during and after eclamptic convulsions in 9 cases. Special reference is made to the improvement in the EEG tracings and clinical picture when the blood pressure is lowered either through the use of caudal analgesia, veratrum viride or by merely allowing sufficient time to elapse. Samples are given of each method and the resulting changes. The following factors were shown: 1. Changes in the EEG were associated with drop in blood pressure, no matter what caused the drop. Slow, high voltage activity was replaced by the more normal low voltage faster material.

2. When the blood pressure did not change, the EEG did not improve.

3. Convulsions were controlled by the drop in blood pressure.

4. Clinical improvement was observed with the drop in blood pressure and the improved EEG pattern.

5. It is suggested that perhaps angiospasm played an important rôle in the eclamptic convulsions.

With the coöperation of Dr. T. S. Hill, Professor of Psychiatry, and Dr. Frank Whitacre, Professor of Obstetrics and Gynecology. The author is also indebted to Dr. Robert A. Hingson and Dr. H. Charles Franklin, who administered the caudal analgesia, and Dr. Walter Loeb, who assisted in the selection of cases and carrying through of the clinical procedures.

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ADMINISTRATION OF MASSIVE DOSES OF VITAMIN P
HESPERIDIN METHYL CHALCONE*

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In the early studies of Szent-Györgyi and co-workers[1] (1936), the designation vitamin P was applied to the group of flavones present in extracts of paprika and lemon peel, which appeared to restore abnormally increased permeability of capillaries. From citrin Mager[13] later isolated eriodictyol rhamnoside, and Higby[10] studied a number of relatively crude flavone preparations and concluded that the eriodictyol glucosides could not be the source of vitamin P activity. Pure hesperidin, pure limonin and pure eriodictyol had no effect on either blood pressure or capillary permeability, but the water-soluble yellow pigment from crude orange hesperidin was found to be active. This was identified as hesperidin chalcone, an unstable derivative, which on methylation was stabilized without affecting its vitamin P activity.

The clinical effect of vitamin P substances has been controversial, and information has been based largely on observations of the petechial index, as measured by the Göthlin test or one of its modifications, and by Scarborough's[15,16] modification of Hecht's[19] negative pressure method. These methods provide at best only crude approximations, as there are several known factors which influence the results and, furthermore, the positive and negative pressure methods do not give comparable results in the same individual. Bell *et al.*[4] tested 142 healthy medical students by the negative pressure method and found low correlation in results, although the tests were consistent within themselves. Beaser, Rudy and Seligman[3] used several methods and concluded that all negative pressure methods were unreliable. Nevertheless, most animal and clinical studies indicate that vitamin P has a definite influence on capillary permeability as distinguished from the capillary lesion in scurvy (increased fragility) which responds to ascorbic acid.

Among the tests for capillary permeability is that described by Landis,[11] and later criticized by Bing,[5] who followed the same technique as Eppinger,[7] and Szent-Györgyi,[1] using a low pressure of 40 mm. Hg. The patient lies for ½ hour with arms horizontal, then the cuff is inflated (in this instance to 40 mm. Hg), and after ½ hour, blood samples are taken from each arm simultaneously and hematocrit and blood protein estimations made. The filtration rate (x) is then determined by a formula: $x = 100 - 100\frac{C_1}{C_2}$, where C_1 and C_2 are the percentile blood volume from the unconstricted and constricted arms, respectively. Bing believed that the experimental error in this procedure was so great that it compromised the results. However, Landis had already stated that

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very low congestive pressures were unaccompanied by any changes great enough to permit conclusions, while at pressures of 80 mm. Hg or more, the capillary wall becomes relatively permeable to fluid. Plass and Rourke[14] applied pressures midway between diastolic and systolic and noted petechial areas below the arm band, accompanied by blood dehydration and an increase in plasma proteins.

Little is known about the absorption, utilization and excretion of vitamin P. The methods for quantitative measurement in body fluids are non-specific. Armentano *et al.*[2] found citrin and eriodictyol to be excreted in the urine and recovered about 50% following intravenous doses of 50 to 100 mg. Gero[8] administered epicatechin orally and observed maximum excretion in 1 hour which then fell rapidly by the end of 3 hours. Only 20% of the dose was recovered. Wilson and co-workers[17] developed a colorimetric test, using borocitric reagent, which appeared to be more specific for materials containing flavones similar in structure to quercetin, and amounts of citrin as low as 2 or 3 μg. could be detected. Flavone determinations were carried out on plant tissues, but no flavone was detected in rabbit liver. The procedure seemed suitable for determination of excretion rates, however, since hesperidin methyl chalcone could be quantitatively recovered following the addition to the urine.

Since the acute toxicity of hesperidin methyl chalcone in mice, both when given orally and intravenously, was found by Chen[16] to be very low and there was no evident chronic toxicity in rats, it seemed expedient to determine whether administration of massive doses of hesperidin methyl chalcone would provide more specific evidence of clinical effect on capillary permeability, as measured by repeated determinations of differences in blood concentrations before and after constriction, and to determine what levels of dosage were required to provide saturation of patients as determined by the excretion of the substances in the urine.

With the exception of Cases J. E. (malignant hypertension) and K. H. (cirrhosis and Banti's disease), the patients chosen for study were in the main from a large group of diabetics showing retinopathy and, as a rule, grossly abnormal petechial indices, as measured by the modification of the Göthlin test described by Lewis, Schneider and McCullagh.[12] The blood pressure cuff was applied to the lower portion of the upper arm, inflated to diastolic level, and allowed to remain 3 minutes. Blood samples were drawn before and after constriction. The petechiae were counted in a 1 inch circle in the antecubital area. Capillary permeability was considered to be increased if more than 20 petechiae were present. In many instances they have consisted of showers over the whole extremity, far too numerous to count.

Observations were made at intervals ranging from 3 days to a week as ascending doses of hesperidin methyl chalcone were administered. Doses as large as 15 gm. were administered orally. Urine blanks of 24 hour samples were first determined, while the patients were kept under observation for several days until the controls showed that no interfering substance was present, and in order to approximate an average normal excretion from natural sources.

Method of Determination in Urine. The procedure of Wilson, Weatherby and Bock[17] depends on the formation by boric acid under anhydrous conditions, of a yellow complex with substances containing the flavone grouping. This color is greatly potentiated by citric acid. Recovery of hesperidin methyl chalcone (water standard) added to urine was found to be 99.6% of the theoretical amount.

Results. Figures 1 to 5 are derived from the clinical and laboratory numerical data plotted in % variation of concentration, which presumably should reflect differences in capillary permeability.

With the exception of Case A. W., there was an apparent decrease in capillary permeability as reflected by diminished per-

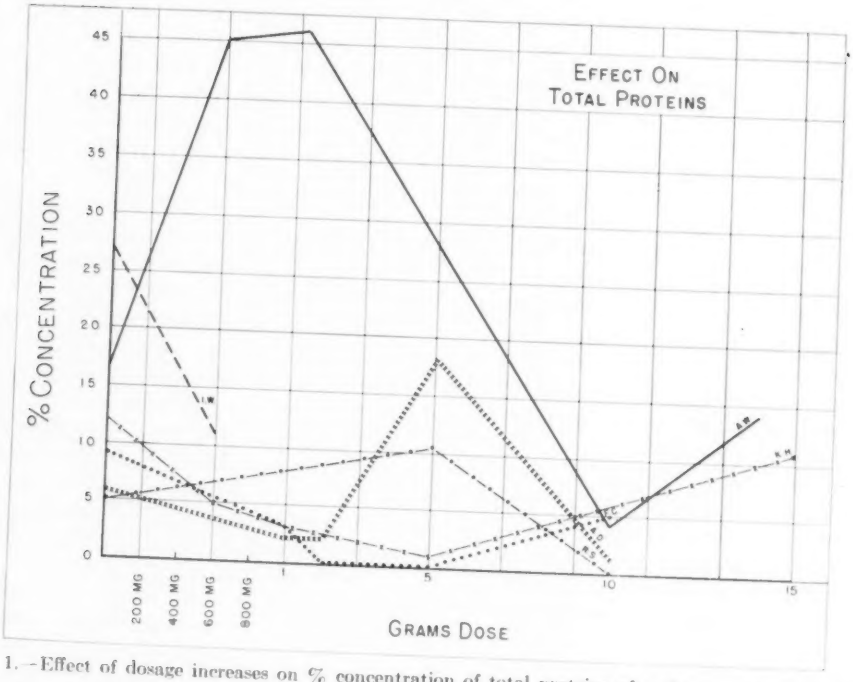

FIG. 1.—Effect of dosage increases on % concentration of total proteins after 3 minutes constriction at diastolic pressure.

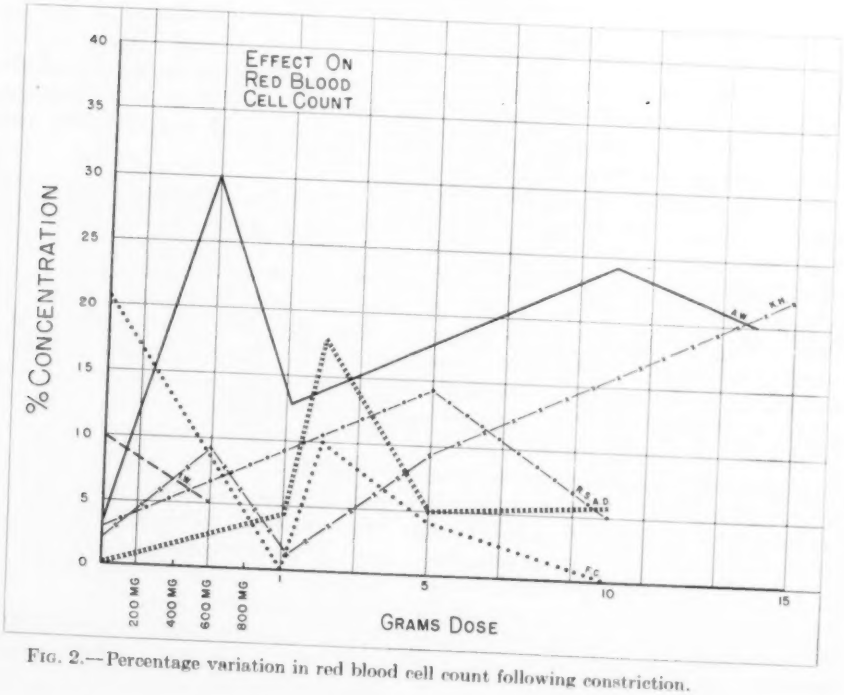

FIG. 2.—Percentage variation in red blood cell count following constriction.

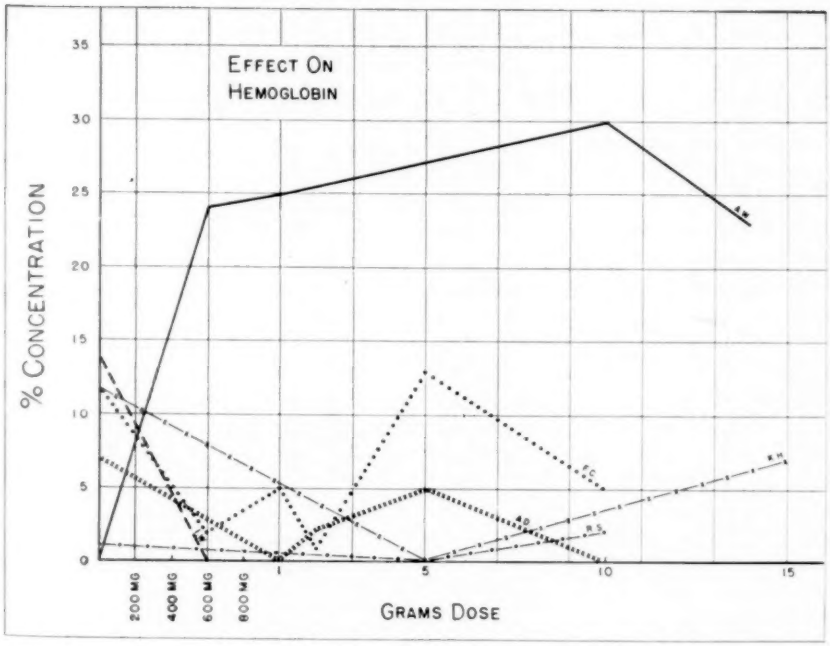

FIG. 3.—Initial apparent reduction in percentage concentration of hemoglobin after constriction followed by reversal of effect as higher dosages reached. Note opposite behavior of Case A. W.

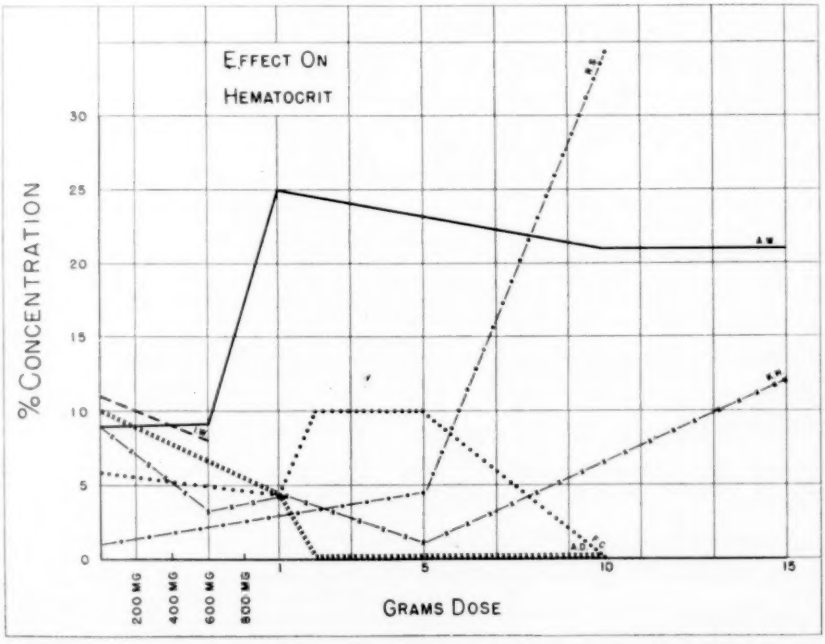

FIG. 4.—Changes in hematocrit after constriction, plotted as % concentration.

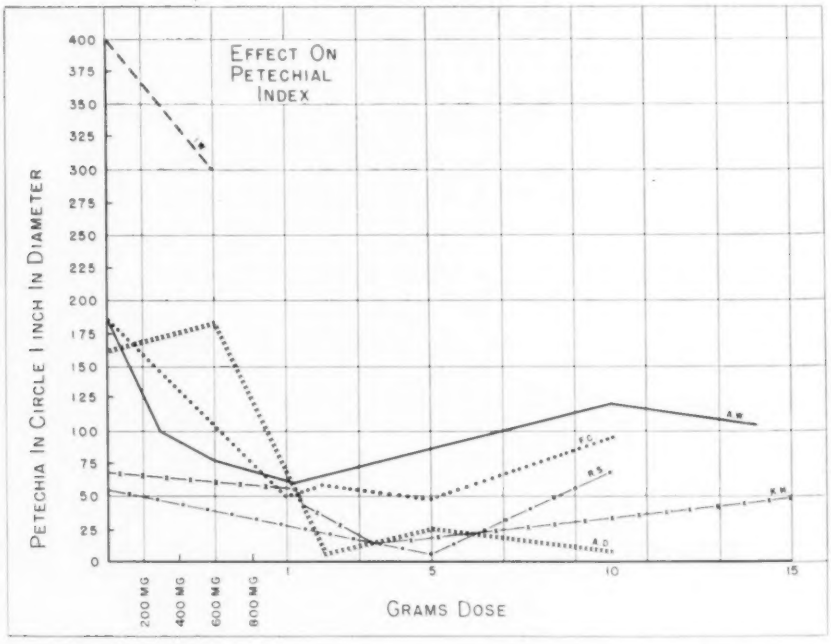

FIG. 5.—Initial reduction in number of petechiæ following constriction, followed by apparent loss of effect from larger doses.

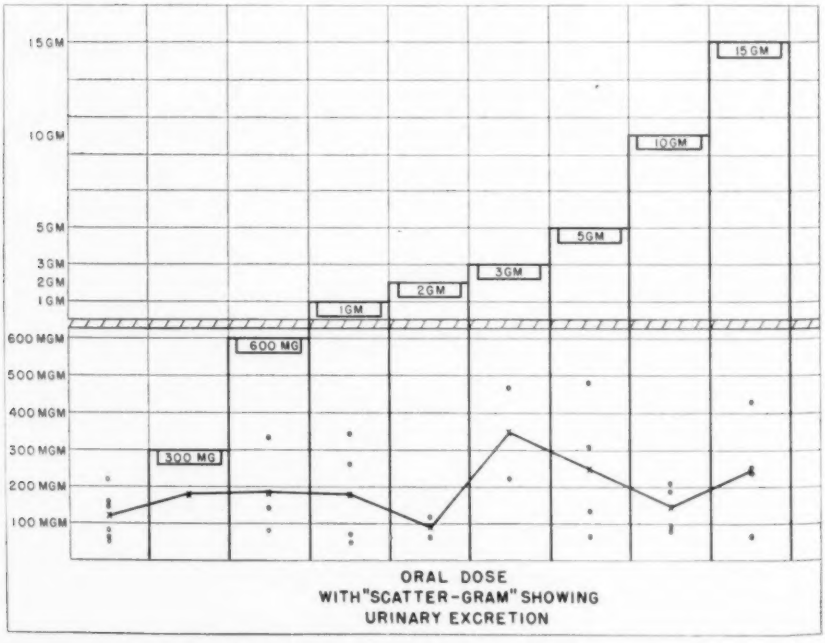

FIG. 6.—Excretion of hesperidin methyl chalcone in urine. There was no quantitative relationship between size of dose and quantity of drug recovered from the urine.

centage concentration of blood proteins as dosage of hesperidin methyl chalcone was progressively increased (Fig. 1). This was followed by a reversal of effect as doses of the order of 5 gm. or more daily were reached. Case A. W. behaved in a strikingly opposite manner. Similar results were observed in the determinations of erythrocyte concentration (Fig. 2), hemoglobin (Fig. 3), and hematocrit (Fig. 4). Only in effect on the petechial index (Fig. 5) was Case A. W. at all typical, and as shown in all the figures the variability of the changes was considerable. The effect on petechial index was the most constant finding, but in this respect also the initial reduction in petechial counts was not regularly maintained as dosage of the drug was progressively increased to levels as high as 15 gm. per day.

The excretion rates of hesperidin methyl chalcone in the urine were disappointing, in that the total quantities recovered were low and bore no quantitative relationship to the quantity of drug administered (Fig. 6).

The total lack of evidence of toxicity following these large doses is noteworthy. One patient stated that it increased the appetite. There were no significant effects on blood pressure, pulse or respiration. Only in one case was hesperidin methyl chalcone administered other than orally. This patient, J. E., age 32, having malignant hypertension, was given 300 mg. intravenously. There was a sharp fall in blood pressure, obvious dyspnea, and complaint of a "bitter taste" in the mouth. The petechial index of 200+ was not altered.

Discussion. It is obvious that these methods fail to establish adequately the effect of hesperidin methyl chalcone on capillary permeability. The changes in concentration of blood proteins, erythrocytes, hemoglobin, hematocrit and petechial index are too variable to be statistically significant. The rather prompt effect on blood concentration which was usually noted and the failure to maintain it suggest the possibility of a tachyphylactic phenomenon, and negate the possibility that doses larger than those that have ordinarily been administered might be more efficacious. This is a curious effect, if indeed the active substance is a vitamin.

Lack of quantitative recovery of hesperidin methyl chalcone in the urine is also of interest. Either the drug is largely destroyed before or during absorption, or it may be utilized, or altered, or conjugated in some manner so that it escapes detection by the test employed.

Conclusions. 1. Studies of blood concentration by estimation of changes in total proteins, hemoglobin, red blood cells and hematocrit before and after constriction are not adequate to determine the effect of hesperidin methyl chalcone on capillary permeability.

2. The drug is not excreted in the urine as such.

3. Hesperidin methyl chalcone has been non-toxic in doses up to 15 gm. daily.

Thanks are due to A. Lee Caldwell and J. Q. Bellard, for earlier work on the excretion of hesperidin methyl chalcone in animals; to T. Woodmansee, for the adaptation of the borocitric method to clinical usage; and to the Resident Staff of the Lilly Laboratories for Clinical Research for their coöperation in making the clinical determinations.

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A SURVEY OF THE TREATMENT OF PERNICIOUS ANEMIA IN RELAPSE:

(A) A COMPARISON OF THE HEMATOPOIETIC RESPONSE TO LIVER EXTRACT AND FOLIC ACID (L-CASEI FACTOR).

(B) LIMITATIONS OF THE RETICULOCYTE RESPONSE AS A MEASURE OF ANTI-PERNICIOUS ANEMIA POTENCY.

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Since synthetic folic acid (*L-casei* factor) became available for general clinical use, several investigators have shown that this newest member of the vitamin B Complex is an active hematopoietic agent for the treatment of megaloblastic anemias. During the past two years, a number of patients with pernicious anemia in relapse have been treated with folic acid, and, as might well be expected, there has been considerable difference of opinion as to its efficacy in the treatment of this disease. It is established that folic acid is a very active hematopoietic agent and is effective in regenerating the blood elements in persons having a megaloblastic type of anemia. It is also certain that folic acid does not prevent or control the central nervous system changes commonly seen in pernicious anemia.

This brief paper has three objects in view:

(1) To make a comparison of the efficacy of folic acid and liver extract in the treatment of pernicious anemia in relapse.

(2) To show the extreme variations in the magnitude of the reticulocyte response encountered in the treatment of pernicious anemia in relapse.

(3) To indicate the limitations of the reticulocyte peak as a "yardstick" in the potency evaluation of anti-pernicious anemia preparations.

Due to the multiplicity of methods used for the determination of hemoglobin, it has seemed best not to present these data. Observations will be limited to data on erythrocyte regeneration and the magnitude of the reticulocyte response.

From our laboratory records* it has been possible to collect complete data for 80 unselected cases of pernicious anemia in relapse treated with parenteral liver extract (of our own manufacture); from several investigators**,

* The author is indebted to: Dr. William P. Murphy, Peter Bent Brigham Hospital, Boston; Dr. J. E. Connery, Third Medical Division, Bellevue Hospital, New York; Dr. William B. Castle, Thorndike Memorial Hospital, Boston; Dr. William Dameshek, Boston Dispensary and Dr. Leo Meyer, Kings County Hospital, Brooklyn, for the data on patients (pernicious anemia in relapse) treated with liver extract.

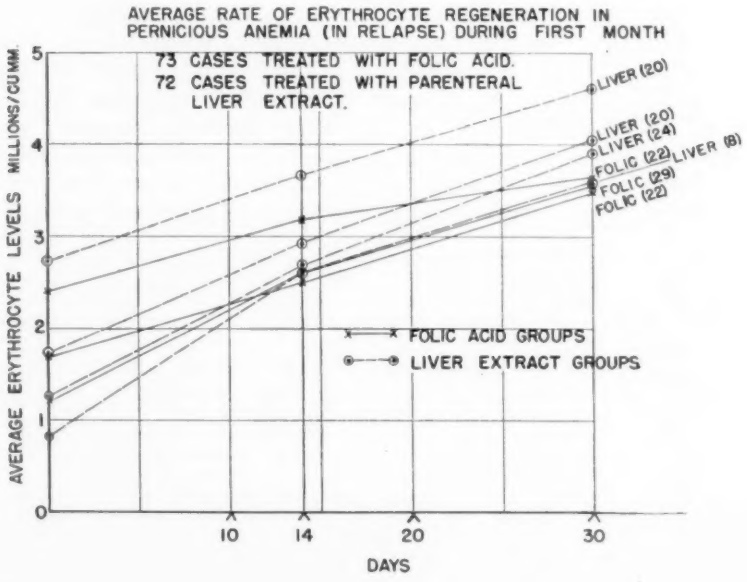
** The following investigators have very kindly supplied data on patients (pernicious anemia in relapse) treated with folic acid: Dr. Luis Amill, St. Luke's Hospital, New York; Dr. William B. Castle, Thorndike Memorial Hospital, Boston; Dr. William Dameshek, Boston Dispensary, Boston; Dr. William P. Murphy, Peter Bent Brigham Hospital, Boston; Dr. Joseph F. Ross, Evans Memorial Hospital, Boston; Dr. Carl V. Moore, Barnes Hospital, St. Louis; Dr. Byron E. Hall, Mayo Clinic, Rochester, Minnesota; Dr. John S. Lawrence, Strong Memorial Hospital, Rochester, N.Y.; Drs. William J. Darby, Edgar Jones and Henry F. Warden, Vanderbilt Hospital, Nashville; Dr. Philip Wagley, Johns Hopkins Hospital, Baltimore; Dr. Grace Goldsmith, Charity Hospital, New Orleans; Dr. David Miller and Dr. William H. Chapple, Edward J. Meyer Memorial Hospital, Buffalo; Dr. M. M. Wintrobe and Dr. G. E. Cartwright, Salt Lake General Hospital, Salt Lake City.

complete data on 73 unselected cases of pernicious anemia in relapse treated with folic acid (parenteral or orally). The number of patients is sufficient for classification according to erythrocyte levels, into 3 statistically significant groups for folic acid and into 5 significant groups for liver extract. The average rate of erythrocyte regeneration for each group is shown in Table I and in Chart I. From a study of the erythrocyte levels attained on the 14th day, it is evident that there is no marked difference between the liver-treated cases and those receiving folic acid. As can be seen from Table I, and better from Chart I, at 30 days there is considerable difference in favor of the liver-treated groups. If, at 30 days, we compare all 80 liver-treated patients with all 73 treated by folic acid, there is an average difference of 0.6 million erythrocytes in favor of those treated with liver extract. For an individual case such a difference would not be significant, but it is of statistical importance when averages of large groups are involved. Also

TABLE 1

Range of Initial Erythrocyte Levels Millions cu./mm.	Number of Patients	Average Erthrocyte Levels Millions cu./mm.			Average daily increment Thousands cu./mm.
			Liver Extract		
0.60–0.99 incl.	8	0.83	2.60	3.57	91
1.00–1.49 incl.	24	1.23	2.69	3.91	89
1.50–1.99 incl.	20	1.70	2.94	4.04	78
2.00–2.40 incl.	8	2.21	3.41	4.40	73
2.50–3.00 incl.	20	2.73	3.68	4.62	63
			Folic Acid		
0.75–0.88* incl.	4	0.82	2.64	3.24	81
0.99–1.49 incl.	29	1.20	2.61	3.56	79
1.50–1.99 incl.	22	1.69	2.50	3.47	59
2.00–3.00 incl.	22	2.42	3.18	3.64	42

* Data not used in analysis—number of patients too small.

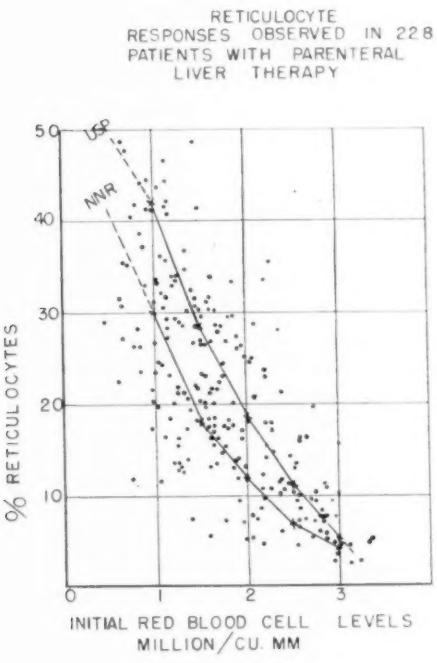


from data presented in Table I it has been possible to calculate the average daily rate of erythrocyte regeneration for each group of patients—these figures also demonstrate that liver extract has produced better results.

During the first years of liver therapy great emphasis was placed upon the character and extent of the reticulocytosis produced by peroral liver therapy. An early sharp rise in the percentage of reticulocytes in the peripheral blood was interpreted as an indication that the extract used was very potent and that a maximum amount of active material had been given. Cohn, Minot, Alles and Salter[2] were the first to formulate relationships between the reticulocytes and erythrocytes in the peripheral blood. In 1930 Riddle[7], using data obtained from 68 patients receiving oral liver therapy, proposed a formula for the expected reticulocyte response at any given level of erythrocytes. In 1933 Bethell and Goldhamer[1] proposed a slightly different formula based on data obtained from the administration of stomach perorally and liver extract given intravenously. In 1938 Isaacs and Friedman[3] proposed a formula based on data obtained from the intramuscular administration of liver extract. Subsequently, the character and extent of the reticulocyte response became the "yardstick" for evaluating the potency of the various preparations of liver or stomach used in the treatment of pernicious anemia. Extensive clinical experience with the intramuscular injection of liver extract has demonstrated several shortcomings in this method of determining potency: (1) extreme variations in the reticulocyte "peaks" produced by the same lot of liver extract in patients having essentially the same initial erythrocyte level; (2) the appearance of a marked reticulocyte "peak" without subsequent and adequate regeneration of erythrocytes; (3) almost complete absence of reticulocytosis, followed by the regeneration of erythrocytes at a maximum rate. As early as 1933 Murphy[4] pointed out the lack of uniformity encountered in the reticulocyte "peaks" and noted that the rate of erythrocyte regeneration was much more constant and suggested that it might well be a better "yardstick" for estimating potency of anti-anemia products. Analysis of Murphy's data for 48 patients shows as much as 300% difference between the high and low reticulocyte peaks observed for a given initial erythrocyte level. Chart 2 contains data for the reticulocyte "peaks" of 227 unselected cases of pernicious anemia in relapse treated with liver extract* given intramuscularly. In order better to evaluate and compare these data, there have been included a curve constructed from data supplied by the U.S. Pharmacopoeia Anti-anemia Preparations Advisory Board[6] and a second curve prepared from data supplied by the Council on Pharmacy and Chemistry[5] in 1936.

In the group of patients treated with liver extract (Chart 2) with erythrocyte levels between 0.50 and 0.99 million/cu. mm., the lowest reticulocyte "peak" was 11.8%, the highest was 48.8%. Between 1.00 and 1.49 levels the lowest observed "peak" was 7.5%, the highest was 48.8%. For levels between 1.50-1.99 the lowest "peak" was 5.3%, the highest was 34%. In the last group, with levels between 2.00-2.50, the lowest "peak" was 4.7%, the highest 28.8%. A study of the data presented in Chart 2 indicates that the figures set forth by the U.S.P. Anti-anemia Preparations Advisory Board for expected reticulocyte "peak" at various erythrocyte levels are too

* The data on reticulocyte "peaks" have been obtained from the clinical assays of liver extract prepared by Lederle Laboratories, Inc.


RETICULOCYTE
RESPONSES OBSERVED IN 228
PATIENTS WITH PARENTERAL
LIVER THERAPY
USP
NNR
50
40
30
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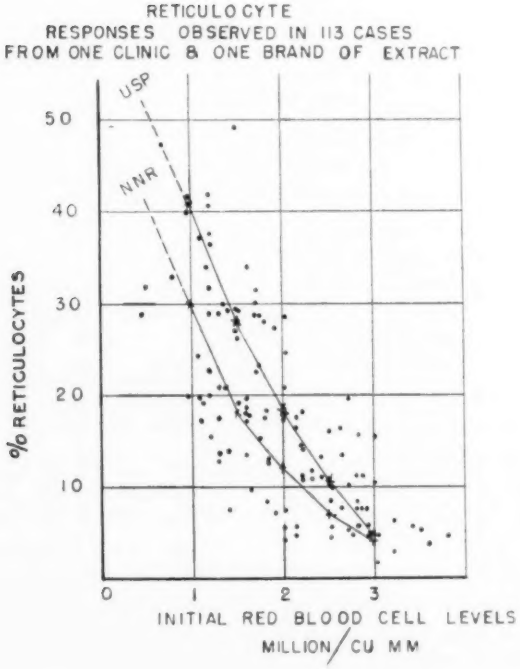
10
% RETICULOCYTES
0
1
2
3
INITIAL RED BLOOD CELL LEVELS
MILLION/CU. MM


RETICULOCYTE
RESPONSES OBSERVED IN 113 CASES
FROM ONE CLINIC & ONE BRAND OF EXTRACT
USP
NNR
50
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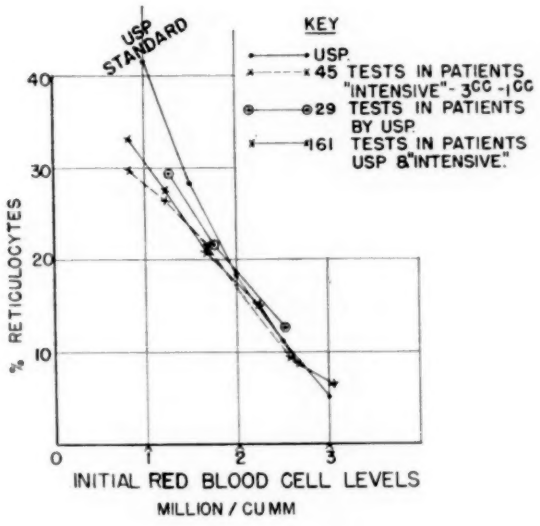
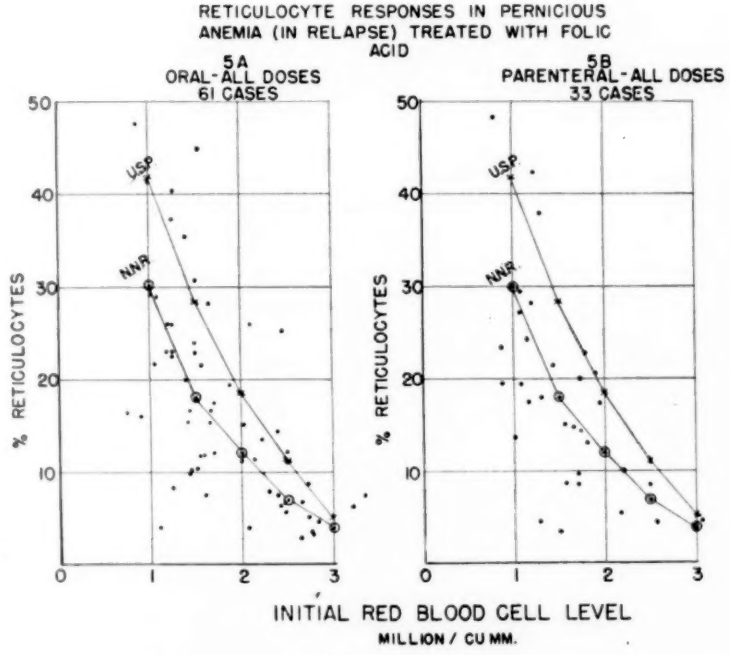




high, particularly for the lower erythrocyte levels (0.5 to 0.99; 1.00 to 1.49; 1.50 to 2.00 millions/cu. mm.). To eliminate, as far as possible, any effects due to different methods of staining and to the counting by different investigators, we have presented the data on reticulocyte "peaks" of 113 patients from one clinic (Chart 3) with all erythrocyte and reticulocyte counts made by one person, and all patients receiving the same brand of liver extract. These data also demonstrate that the U.S.P. "standards" are too

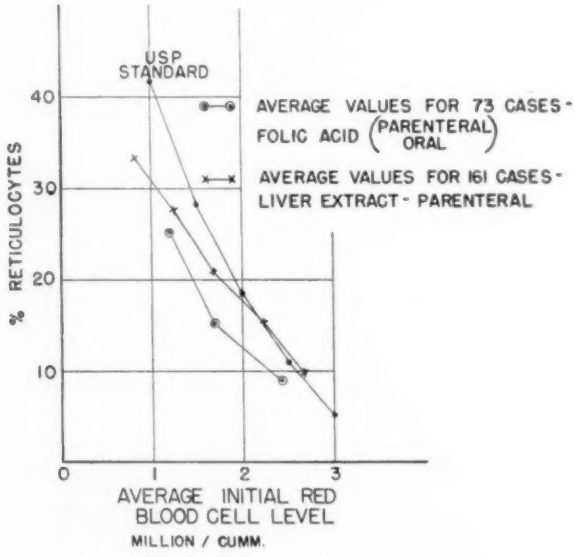
high as only 46 out of the 113 responses meet the prescribed U.S.P. requirements. Chart 4 shows the U.S.P. standard curve; data for 29 tests made by the U.S.P. method; 45 tests based on intensive liver therapy (pre-U.S.P.) and a curve based on a collection of 161 assays of liver extract. The composite curve based on 161 assays suggests that it might be desirable to modify the "standards" set forth by the U.S.P. Anti-anemia Preparations Advisory Board, somewhat as follows:

Erythrocyte Levels Present	U.S.P. % Reticulocytes	Proposed Revision % Reticulocytes
1.00	41.8	31.0
1.00–1.50	28.4	24.0
1.50–2.00	18.6	18.0
2.00–2.50	11.1	11.0
2.50–3.00	5.1	5.0

The above changes occupy a point between the early NNR standards and those proposed by the U.S.P. Board and are more in accord with clinical observations made by a number of investigators.

Most of the reticulocyte "peaks" observed after the administration of folic acid are lower than those observed with liver therapy. Chart 5 shows data obtained from 94 unselected cases, 61 receiving the material perorally (5A) and 33 parenterally (5B). In the peroral group 45 of the 61 reticulocyte peaks fall below the U.S.P. standard curve of expectancy—31 are even below the original figures proposed in N.N.R. of 1936. In 26 of the 31 cases receiving parenteral folic acid therapy the reticulocyte peaks were below the U.S.P. curve—19 below the N.N.R. values. A reticulocyte response curve based on 161 cases treated with liver extract and a similar curve based on 73 cases treated with folic acid, presented in Chart 6, afford a comparison of the reticulocytosis produced by the two products.

Discussion. From the data presented in Charts 2, 3, 4, 6, it is evident that the reticulocytosis produced by the administration of liver extract is subject to extreme variations. Since less than 50% of the "peaks" of the 228 cases equal or exceed the standard response curve, it is less valuable than is generally believed as a means of



evaluating the potency of anti-anemia preparations.

Summary. A comparison of the hematopoietic response caused by liver extract or folic acid over a 30-day period, in patients with Addisonian pernicious anemia in relapse, indicates that the rate of erythrocyte regeneration is higher with liver extract than with folic acid.

The variations in the reticulocyte peak observed at any given erythrocyte level are too great to permit use of this physiological reaction as a quantitative measure of the potency of anti-anemia preparations. Certain revisions (for the lower erythrocyte levels) for U.S.P. "standards" are suggested.

Usually the reticulocyte "peak" is much lower with folic acid than has been found for liver extract.

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SEVERE PAROXYSMAL CARDIAC PAIN AS A PRODROME IN IDIOPATHIC EPILEPSY

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An "aura" is generally considered to precede the convulsion in epilepsy by 1 to 5 minutes, rarely more. Usually the aura instantly announces the coming fit. Prodromata, on the other hand, are symptoms which may occur hours or days before the actual fit. Yet distinction may not prove a simple matter, for some of the prodromal symptoms may continue virtually to the moment of onset while others are placed by different observers in different categories.[8]

In general, prodromata fall into one of 4 groups: (1) motor, (2) sensory, (3) psychical and (4) visceral.

The most common of all are the motor type, and of these, myoclonic twitches or sudden starts affecting one or more limbs occur most frequently. This motor jactitation occurs during the early morning hours or when rising out of bed.

The sensory phenomena are manifested by headache, vertigo, recurrent flashes of light or tinnitus aurium.

The psychical type demonstrate alteration in mood, irritability, depression, a desire to be left alone, or anxiety.

The visceral prodromata may manifest themselves by anorexia or the reverse (ravenous appetite), dyspepsia, flatulence, cutaneous eruptions (erythema, pruritus), malaise, a sense of oppression or tightness across the anterior aspect of the chest. The visceral group comprises symptoms of circulatory, respiratory, vasomotor, vesical, rectal and pupillary nature. It is apparent, therefore, that disturbance in function occurs in organs innervated by the vagus nerve and presumably starts in vagal nuclei on the floor of the fourth ventricle and adjacent to the vasomotor centers.

Obscurities arise when one approaches the question of epileptic seizures of visceromotor or viscerosensory origin. On general grounds, participation of these centers in epileptiform manifestations must be conceded. The sudden pallor of many cases with petit mal and the "nervous faints" are instances in point. Earlier writers[3] termed these episodes "vagal or vasovagal attacks" and because of their periodicity they were thought to be of the nature of epileptiform discharges in these lower centers.

Severe paroxysmal pain of the characteristic cardiac type was observed as a prodromal manifestation of epilepsy in 2 young women, one of whom had rheumatic heart disease which made the etiology of the cardic pain more perplexing.

Case Reports. CASE 1. V. J., a 34-year old colored female, stated that on Nov. 25, 1947, at 1 p. m. while leaving a cafeteria in the building where she was employed and climbing up one flight of stairs she experienced a constricting pain over the precordium which radiated to the left arm and scapula. This was followed by shortness of breath and unconsciousness. She was then brought to the company doctor where she regained consciousness, but was still orthopneic and dyspneic. She was given amyl nitrite inhalations and morphine sulfate

hypodermically, but showed no improvement, and so transfer to the hospital was advised. The dyspnea persisted in the admitting room of the hospital, and she was sent to a medical ward with a tentative diagnosis of acute coronary insufficiency.

Previous History. The patient stated that she had been more or less sickly all her life and was troubled with headaches which were made worse during menstrual periods. There was no history of epilepsy or migraine in the family and she had given birth to 3 children, the last a Mongolian idiot. There was no history of rheumatic fever or syphilis. In February, 1944, a hysterectomy was done and one year later patient began to have typical "grand mal" epileptic seizures. The aura, at first, consisted of a "queer feeling" throughout the body. At first she had about 3 seizures a month. From March until June, 1945, she was at a health resort in Arizona, but continued to have the same number of convulsions. On one occasion she attempted suicide because of inability to hold a job on account of her illness. At the time of her admission to the hospital she had been taking dilantin 1.5 gr. t.i.d. and phenobarbital gr. 1.5 as prescribed by a dispensary that she had been attending. Despite medication she continued to have convulsions at irregular intervals. This was the first time the convulsion was preceded by pain over the heart.

Course and Progress. The patient was very intelligent and cooperative. She was anxious to do anything that would make her well. While at the hospital she was observed during several typical attacks. She would suddenly have severe precordial distress which was described as a "pressing" feeling which radiated to the left arm and scapula. This would be followed by dyspnea and orthopnea. She was given various cardiac drugs such as nitroglycerin, amyl nitrite and aminophylline intravenously with no apparent effect. After a period of from 15 to 30 minutes she would go into a typical grand mal convulsion. Status epilepticus occurred on one occasion while in the hospital which was controlled by sodium amytal intravenously.

Examination disclosed a thin, apprehensive, colored female. The pupils reacted to light andoon accommodation, fundi were normal. She had normal fields of vision and active corneal reflexes. Motor power was good. The superficial reflexes were normal and the deep reflexes were hyperactive. Light touch, position and stereognosis were normal. Gait showed good coordination. The heart and lungs were normal. Spinal fluid examination revealed the following: pressure 80mm., clear and colorless, normal dynamics, cell count 4, Pandy and colloidal gold negative, Wassermann negative. Blood count and blood Wassermann were negative. The chest X-ray and electrocardiogram were normal. X-rays of skull in anteroposterior and lateral views were normal. Electroencephalogram revealed low voltage, 11 to 12 per second activity. Parietal and frontal areas showed bursts of 6 to 8-per second and bursts of 4 to 6-per second waves, moderate build-up with hyperventilation. Impression: moderately abnormal electroencephalogram with frequent slow waves most marked in frontal and parietal areas.

Case 2. S. D., a 34-year old white female, married, one child, stated that on Christmas night, 1946, while reading a magazine, she was suddenly seized with a severe agonizing pain over the lower sternal and precordial areas which radiated down the left arm as far as the wrist. She stated the pain was unbearable and begged for relief. Her face was pale and covered with clammy perspiration. She was sitting up in bed with her head thrown backward as if this were the only position that would afford some degree of relief. Tachypnea was present, but seemed to be a result of the severe pain. The temperature and pulse and blood pressure were normal. She was given morphine sulfate and atropine hypodermically and after 15 minutes, the condition remained unchanged. She was then taken to the hospital, given oxygen and the attack gradually subsided.

Previous History. Patient was an adopted child and had no information about her parents. She was always highly emotional and given to fainting spells. There was no history of rheumatic fever

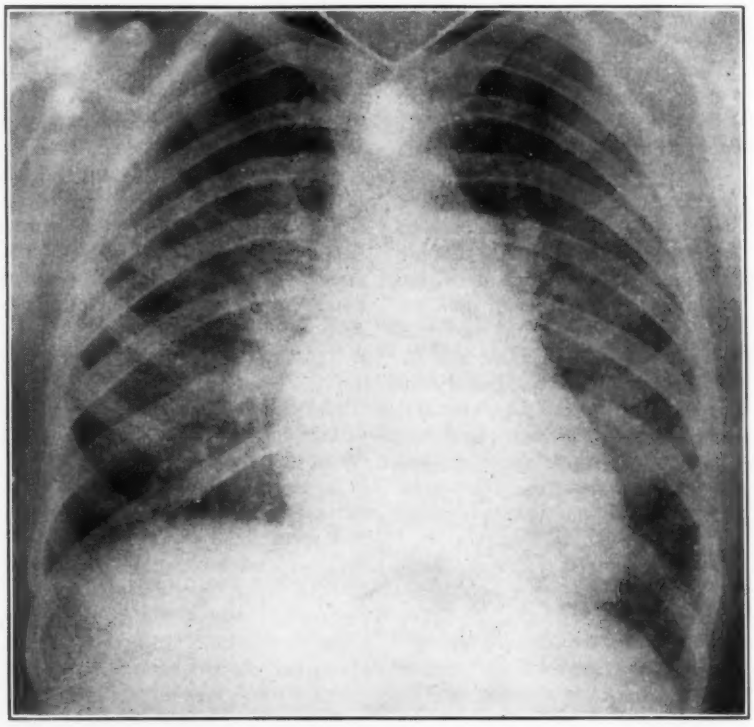

Fig. 1.—Case 2. Chest X-ray showing enlargement of the left ventricle and a fullness in the region of the pulmonary conus; Heavy hilar shadows and thickened interlobar fissure.

in childhood. At the age of 17 she eloped and was happily married. At the time of her pregnancy, heart murmurs were discovered and she was advised to take things easy. However, she was weak for 5 months after delivery, but for the next 4 or 5 years was fairly well. There was no history of cardiac failure at any time.

Physical Examination. On Dec. 26, the day after admission to the hospital, the patient sat up in bed as if nothing had happened. She was naturally sallow in color. The temperature, pulse and blood pressure were normal. No rales were heard. On percussion the heart was enlarged to the left and an increased area of dullness was noted in the 3rd left interspace adjacent to the sternum. At the apex a distinct presystolic thrill was palpable. On auscultation over this area, a low pitched, rumbling murmur beginning in mid-diastole with presystolic accentuation and a short systolic murmur were audible. An early soft diastolic murmur was heard over Erb's point and the puemonic second sound was accentuated..

The chest X-ray, (Fig. 1) Jan. 3, 1947, revealed a prominence of the pulmonary bow and the left heart was definitely increased in diameter. Hilar shadows were heavy in each lung field and air passages were re-enforced. The right dome of the diaphragm was hazy in outline. The interlobar pleura was visualized in the middle of the right lung field. The skull X-ray was negative.

Examination of the urine was negative. The Kahn and Wassermann tests were negative. The blood findings were as follows: Hemoglobin 11.5 gm., red blood cells, 3,800,000, white cells, 13,100, with 70% neutrophils, 26% lymphocytes and 4% monocytes.

Course and Description of Typical Attack. About 3 days after admission to the hospital the patient was suddenly awakened in the early morning hours by an agonizing, excruciating precordial pain

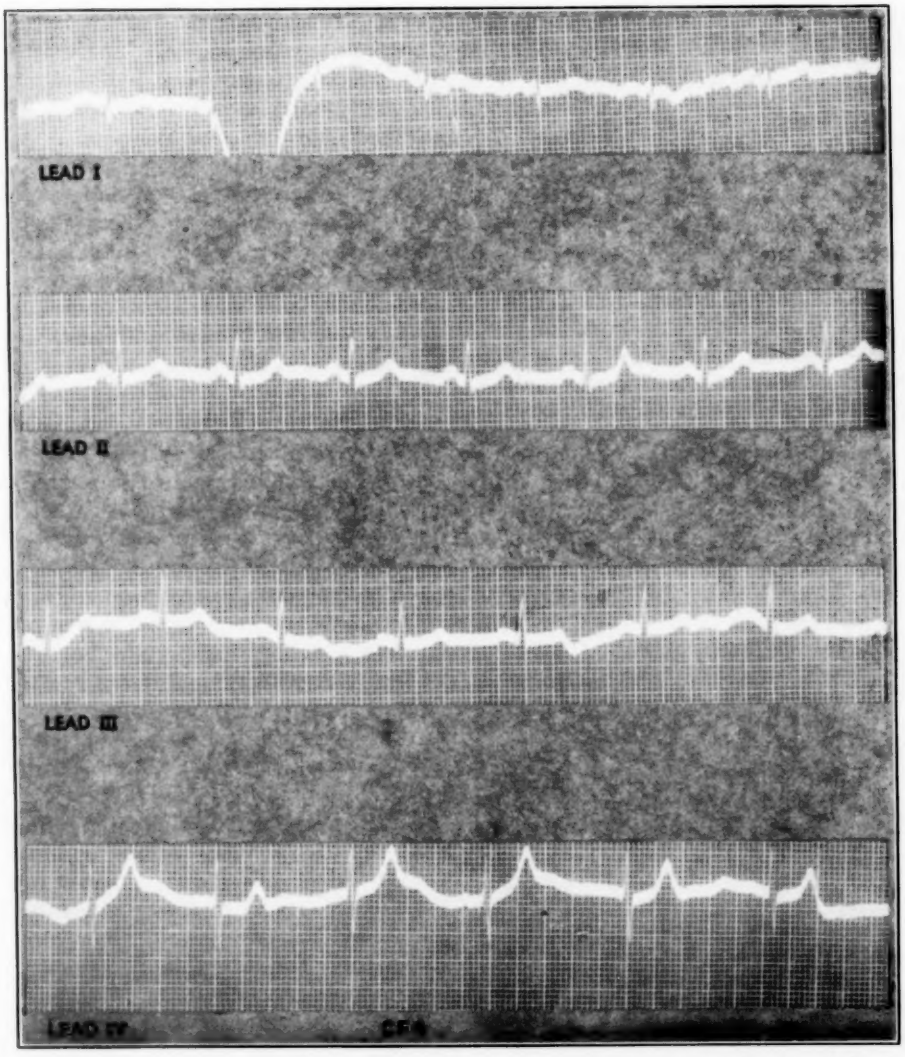

Fig. 2.—Case 2. Electrocardiogram taken during the paroxysm of pain, showing slight depression of S-T segment in CF_4. In addition, there is slight depression of $S\text{-}T_2$, low to inverted T waves in Lead I, and right axis shift.

which radiated to the left shoulder and left arm. She was sitting up in bed clutching her left breast and at the same time tearing her nightgown into shreds. Her face was pale and slightly cyanotic about the lips and her forehead covered with beads of perspiration. Her head was extended backward in an opisthotonus position. She made attempts to get out of bed as it appeared as though walking would relieve her. She was markedly dyspneic but no rales were heard. Several of the hospital personnel were about her bed at the time of the pain, but she did not seem cognizant of their presence. Various drugs were tried, such as sublingual administration of nitroglycerine, amyl nitrite, and aminophylline intravenously, but these were of no avail. An electrocardiogram (Fig. 2) taken at this time showed only very slight depression of $S\text{-}T_4$ and this was not thought deep enough to be

diagnostic. After oxygen administration, the attack gradually subsided, although when these agents were withheld in other attacks they subsided in approximately the same length of time. The patient seemed confused and bewildered after the attack and seemed surprised to note the look of concern on the faces of those about her. There then followed an aftermath of somnolence and much weakness so that she was unable to get out of bed for days at a time. She had several of these episodes in the month she remained at the hospital, some being milder than others. There was always hyperesthesia over the apical region of the heart.

It was later learned from the husband that in 1941 he had come home from work one night and found his wife lying on the couch in a "trance" as he called it. A local doctor was called who diagnosed a nervous disorder and ordered the patient to the hospital. The patient remained in the hospital for 10 days and had no attacks of any kind. She was discharged undiagnosed. The urinalysis and blood count were normal. An intracerebral lesion was suspected and skull X-rays were negative. The sella turcica was small but within normal limits. Spinal fluid examination revealed the following: Wassermann negative, sugar 76, protein 38, Lange colloidal gold test 1111100000.

The electrocardiogram at that time showed sinus bradycardia, normal axis and rather prominent T waves in the standard and precordial leads.

It was later learned that at times she would complain of being tired, weak and warm and would lie down. Right after this she would not respond to questions and her husband noted a vacant look or fixed expression with facial pallor and slight twitches of the lips and tongue. On one occasion while tending to her baby she suddenly found herself on the floor with a "goose egg" on the back of her head.

Discussion. Pain over the heart may be due not only to pathologic conditions in the heart or aorta, but also to abnormal states of the nervous system, both cerebrospinal and vegetative. Therefore, in an analysis of altered cardiac sensation the existence of extraneous factors entirely apart from the disease under investigation must be recognized and their relative importance in the production of symptoms must be evaluated.

From a description of these 2 cases it is obvious that the various manifestations they exhibit place them in a different category from that of patients with so-called classical symptoms of angina pectoris. First, the pain was spontaneous and not preceded by effort or emotion. The distress had no relationship to meals and was never preceded by nausea or vomiting.. Rest did not offer any relief. It is also of interest in that the attacks occurred over a certain "crucial" period, and then the patient might remain free from pain for months to years.

The first case, however, closely simulated a true anginal syndrome, and in fact, the patient was treated as an acute coronary occlusion in 2 different institutions. While under observation at the hospital, it was noted that each convulsion was preceded by a paroxysm of chest pain of 15 to 60 minutes duration and it was interesting that each resident physician who saw her in the early attack administered nitrites, aminophylline, oxygen and other cardiac drugs. These measures seemed to have no effect on the pain. After each seizure she would fall asleep for several hours and when she awoke the pain had disappeared.

In the second case, the cause of the pain was a little more difficult to analyze. The patient was known to have chronic rheumatic heart disease with mitral stenosis and insufficiency and aortic regurgitation. It is commonly known[5,7] that aortic insufficiency may be associated with typical attacks of angina pectoris. This has been explained as due to the low diastolic pressure which results in incomplete filling of the coronary arteries and thus

produces a relative anoxemia of the heart. Even uncomplicated mitral stenosis[1,2,7] may give rise to an anginal syndrome probably due to inadequate coronary circulation on effort. Pain in rheumatic heart disease may also be due to (1) pericarditis, (2) active rheumatic heart disease with coronary artery lesions[4], or (3) added effort of paroxysmal tachycardia, paroxysmal flutter or fibrillation, or in congestive heart failure.

Schwartz[6] described a form of severe paroxysmal cardiac pain in 5 young adults all of whom had rheumatic heart disease with aortic insufficiency. His cases were also characterized by violent palpitation of the heart, vasomotor phenomena, marked pulsations of the peripheral vessels and increased blood pressure. These patients showed various psychopathic stigmata and some were given to syncopal attacks. However, he did not consider any relationship of these symptoms to epilepsy.

Gowers[3] states that a cardiac aura is not common in epilepsy. He cites the case of a boy, aged 16 years, subject to fainting spells, each preceded by stabbing pains over the heart followed by loss of consciousness. On return of consciousness after a minute, he struggled and had to be held down, evidently in the hysteroid state that so often follows minor epilepsy, but never occurs after cardiac syncope. Yet the case had first been regarded as one of simple "cardiac faints" on account of the initial pain, which was really an epiliptic aura.

Summary. Two cases of idiopathic epilepsy are described in which the prodromata consisted of severe paroxysmal cardiac pain simulating true angina pectoris. In one case, though rheumatic aortic insufficiency and mitral stenosis and insufficiency were present, it was felt that these valvular lesions did not contribute to the angina pectoris syndrome.

It should be emphasized that severe precordial pain may be due not only to intrinsic disease of the heart or aorta, but also to abnormal states of the nervous system.

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DYNAMICS OF THE HYPOGLYCEMIC REACTION

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Clinical manifestations attributable to an abnormal lowering of the blood sugar were observed even before the discovery of insulin. In 1921, Joslin[65a] reported several cases of hypoglycemia in extremely undernourished diabetics, one of whom died with a blood sugar of 40 mg. per 100 cc. One year later, Woodyatt[121] observed a patient with diabetes who died in hypoglycemic convulsions; he also referred to a fatal case of hypoglycemia noted by Williams in whom no insulin was used. Harrop[50] cited a patient with severe diabetes and extreme emaciation observed by Herman; the blood sugar 5 hours before death was 17 mg. per 100 c.c. The first description of hypoglycemic reactions in animals injected with insulin was given by Banting, Best and their collaborators[7] and was soon followed by reports of Banting et al.[8] on the occurrence of such reactions in diabetics treated with insulin. Shortly thereafter it was realized that the described symptom-complex might develop in non-starved individuals even when no exogenous insulin was taken. Harris[47] was the first to suggest that spontaneous hypoglycemia might be produced by excessive secretion of endogenous insulin and he proposed the term of hyperinsulinism for this disease entity. In 1927, Wilder et al.[120] reported the first case of hyperinsulinism resulting from pancreatic carcinoma.

Since it was noted that (a) an overdose of insulin produced a critical depression of the blood sugar accompanied by a group of characteristic clinical symptoms and (b) the spontaneous occurrence of such symptoms was associated with hypoglycemia, the subnormal blood sugar was assumed to be the cause of the symptoms. This explanation soon proved unsatisfactory since on occasions after the administration of insulin, hypoglycemic symptoms were present even though the

blood sugar was not critically lowered. In other instances, symptoms were absent even when the blood sugar was markedly depressed. Again, Banting, Best and their associates[7,8,40] were the first to make such observations. Similar findings were later described by many others in various types of experimental and clinical hypoglycemia[27,31,32,33,48,49,50,52,62,63,65b,66a,67,73,79,86,92,93,99,103,105,111,112,114,116,119a].

To account for the lack of parallelism between the clinical and laboratory findings in hypoglycemia, it was suggested that in the absence of critically low blood sugar levels, symptoms were produced by a rapid fall of the blood sugar[3,21,79,94,112,119b]. However, the question why some patients remained symptom-free in spite of a marked depression of the blood sugar was left unanswered.

Two explanations were offered to account for the mechanism whereby lowering of the blood sugar produced clinical symptoms. Since some of the symptoms were similar to those which followed the injection of epinephrine (mydriasis, tremor, tachycardia, etc.), some workers[12,34,71,72,112] ascribed the hypoglycemic symptoms to a secondary release of epinephrine. Other investigators implicated the central nervous system. In 1928, Joslin[65c] stated "It may possibly be that through the lowering of blood sugar, certain oxidative processes become depressed to such a degree that the brain cells are affected in much the same manner as in asphyxia." This view found support in the studies of Lennox[77] and of Himwich and Nahum[56] which disclosed that the respiratory quotient of the brain approximated unity, a finding which indicated that the brain derived its energy chiefly from carbohydrate. Thus, a diminished supply of glucose to the brain such as might occur in hypoglycemia would reduce the cerebral metabolism and thus produce the clinical picture of hypoglycemia. From observations made during insulin shock therapy, Frostig[42] and Himwich[54] divided the symptoms of acute hypoglycemia into 5 phases and correlated the sequence of these phases with the depression of the metabolic rate at various levels of the brain.

More recently, it was found that the effect of hypoglycemia on the function of the brain was an indirect one. Holmes[59], Dameshek et al.[28] and particularly Himwich and Fazekas[55] showed that low blood sugar values diminished cerebral oxidative metabolism, whereas the administration of glucose was followed by an increase in the oxygen uptake by the brain. Cerebral anoxia as the immediate factor in the production of hypoglycemic symptoms was further accentuated by other studies of Himwich and by those of Gellhorn and Kessler[43].

Feldberg[35,36] noted that the synthesis of acetylcholine by brain tissue was stimulated by low concentrations of glucose and inhibited when the sugar content of the medium was as high or higher than that in normal blood. Since acetylcholine was a convulsant, he suggested that the increased production and release of acetylcholine by the nervous system during hypoglycemia might account for part of the picture of the hypoglycemic reaction.

From the foregoing, it appears that much emphasis has been placed on the variations in blood sugar during hypoglycemic reactions and not enough on the dynamics of cerebral sugar metabolism. It is obvious, however, that the utilization of sugar by the brain cannot be measured by the rate of supply of glucose but rather by the magnitude of cerebral consumption of this fuel in relation to the energetic needs of the brain. While it is readily understood that a low blood sugar may lead to carbohydrate starvation of the central nervous system accom-

panied by clinical symptoms of hypoglycemia, the absence of the hypoglycemic reaction even when the blood sugar is critically depressed can be explained only by assuming that (a) the decrease in blood sugar is not necessarily equivalent to a decrease in brain sugar and (b) a low blood sugar does not greatly affect a brain whose energy requirements are relatively low.

Evidence is available to support the view that the cerebral consumption of sugar does not parallel blood sugar variations. Kerr and Best[68] postulated that as a result of utilization of sugar by the central nervous system, the sugar content of the brain is always lower than the blood sugar level. On the other hand, Himwich and Fazekas[55] in experiments with dogs injected with insulin found a glucose uptake of 13.1 mg. per 100 cc. when the blood sugar ranged from 110 to 62 mg. per 100 cc. and only a slight reduction in uptake to 12.5 mg. per 100 cc. when the blood sugar was depressed to between 46 and 25 mg. per 100 cc. As for variations in cerebral energy requirements, Cannon et al.[19] observed that in cats deep chloralose anesthesia reduced or abolished the insulin reaction although it did not prevent the fall of the blood sugar. Högler[57] demonstrated that during veronal or luminal anesthesia in rabbits even a profound hypoglycemia was not accompanied by convulsions. Of particular significance were the observations of Harrison[49] who in diabetic children under 12 years of age found insulin reactions to occur at a lower blood sugar level than in adults. Similarly, White[115] noted the infrequent occurrence of hypoglycemic reactions in babies with subnormal blood sugars. Himwich[54] in commenting on White's paper suggested that since the metabolic rate of a newborn infant was much lower than in the adult, the energy expenditure of the brain of the infant must of necessity also be much lower than in the adult.

On the other hand, it is conceivable that with normal blood sugar values the rate of supply of sugar to the brain may be decreased beneath the cerebral metabolic requirement. Although there is no evidence available to support such a view, this hypothesis is suggested by analogy on the basis of studies on the distribution of fructose between arterial blood and brain tissue. Klein et al.[70] in experiments with eviscerated rats recently demonstrated that the proportion of intravenously administered fructose which passes to the brain is so small that this sugar cannot maintain normal brain function. By assuming that passage of glucose to the brain may under certain circumstances be similarly disturbed, one might explain the occurrence of hypoglycemic manifestations in absence of laboratory evidence of hypoglycemia.

Another dynamic factor that must be considered is the ability of the brain not only to absorb but also to release sugar. Himwich and Fazekas[55] reported that when the blood sugar was raised to high levels by the intravenous administration of glucose, the cerebral sugar uptake was almost doubled (23.5 mg. per 100 cc.). When the blood sugar was rapidly raised and then quickly reduced by administration of both glucose and insulin, the brain secreted glucose into the blood stream during the fall of the blood sugar, with the result that more sugar was found in venous than in arterial blood. These data are in keeping with the earlier observations of Rosenow[102] who in a case of spontaneous hypoglycemia found no arterio-venous difference in blood sugar and with those of Holzer and Klein[60] and Butt and Keys[18] who in hypoglycemia after insulin found the oxygen saturation of venous blood to be of the same magnitude or even higher than that of

arterial blood. It is to be noted, however, that these writers ascribed such arterialization of the venous blood to an increased blood flow whereby less oxygen would be given off by the blood to the tissues rather than to the activity of the tissues themselves.

Mention should also be made of the equilibrium which exists between the sugar concentration in the blood and in the cerebral fluids. Under normal conditions, the sugar content of the blood is higher than that of the cerebrospinal fluid, the ratio being roughly 2:1. In insulin hypoglycemia, the sugar concentration in the cerebrospinal fluid usually remains unchanged or it may be increased so that the ratio becomes reversed[117]. During hypoglycemic reactions, Gravano[46] found the concentration of glucose in blood and cerebrospinal fluid to be 40 and 163 mg. per 100 cc., respectively, and Sigwald[105] 65 and 100 mg. per 100 c.c.

Constriction of the cerebral arterioles and capillaries may occur in severe hypoglycemia. In irreversible insulin coma, Ferraro and Jervis[39] found endothelial proliferation and obliteration of small vessels and capillaries in the cerebral cortex. These vascular alterations were considered to be a factor in the production of brain anoxia. Reitman[96] reported on the efficacy of vasodilator drugs such as nicotinic acid and amyl nitrite in abolishing hypoglycemic convulsions. More recently, Sindell[106] published his findings on 3 patients with hypoglycemic coma who recovered following the use of amyl nitrite by inhalation. However, cerebral vasoconstriction does not seem to play a significant part in the causation of milder hypoglycemic reactions since according to Cobb and Lennox[20] the cerebral circulation is not impaired during hypoglycemia as long as there is no loss of consciousness. These writers also ascribe the electroencephalographic changes accompanying subnormal blood sugars not to circulatory abnormalities but to changes in blood chemistry.

From the foregoing, it is evident that carbohydrate metabolism of the brain is subject to a number of factors. The variations of glucose in the blood are undoubtedly important but of major significance appears to be the active participation of the brain in controlling its own consumption of glucose. This may represent a mechanism whereby the brain tissue can protect itself against a dearth of this nutritive substrate. This dynamic concept of cerebral carbohydrate metabolism may provide a better understanding of the hypoglycemic reaction. It may explain the reported inconsistencies between clinical and laboratory findings in hypoglycemia since it may account for both the absence of symptoms with distinctly hypoglycemic levels as well as for the occurrence of symptoms without subnormal blood sugar levels. In accordance with this concept, the hypoglycemic symptoms may develop (a) when the decrease in blood sugar is very profound and cannot be compensated for by an increased cerebral glucose consumption, (b) when the transfer of glucose from the blood to the brain is appreciably reduced and (c) when the brain tissue is unable to absorb adequate amounts of sugar or to utilize it properly even though the sugar may be supplied at a normal rate. In all these instances, glucose consumption by the brain is diminished below the cerebral metabolic needs. Such cerebral glycopenia may then produce the hypoglycemic reaction either by way of cerebral anoxia, by disturbances in the metabolism of acetylcholine or possibly by still another unknown mechanism.

Pseudohypoglycemic Reactions. Symptoms usually associated with hypoglycemia may occur in various conditions in which the carbohydrate

metabolism is not primarily involved, such as epilepsy and hypoparathyroidism[32]. It is significant that in these conditions disturbances of brain function are present as revealed by abnormalities of the electroencephalogram. With regard to epilepsy, the basic nature of this disease is now characterized as cerebral dysrhythmia and further elaboration here appears unnecessary. In hypoparathyroidism, emphasis is usually laid on the depression of serum calcium since this element is known to be essential for the normal function of nerve tissue and for the maintenance of normal neuromuscular excitability. Interestingly enough, the presence of cerebral dysfunction was recently reported in tetany. Albright et al.[1] observed a case of idiopathic hypoparathyroidism in which the electroencephalographic tracing was consistent with the diagnosis of epilepsy. The patient was treated unsuccessfully for epilepsy for many years. Her seizures became less frequent and less severe following antitetanic treatment with dihydrotachysterol (hytakerol, A.T. 10). Odoriz et al.[90] described the electroencephalographic abnormalities in hypoparathyroidism as consisting of a diminution in alpha activity and appearance of single spikes as well as trains of 2 to 3 per second waves. Taubenhaus and Engle[110] reported a case of hypoparathyroidism associated with grand mal epilepsy. Correction of the hypocalcemia not only eliminated the tetanic and epileptic symptoms but also diminished the electroencephalographic abnormalities.

The association of hypoglycemia with hypocalcemia and electrocerebral dysfunction was recently reported by one of us[32]. Therapy aimed at only one of the coexisting conditions was followed by partial improvement whereas complete freedom from symptoms was obtained when the treatment was directed at all the associated conditions. It was not possible to ascertain whether some of the reactions were produced solely by the cerebral dysfunction although such a possibility was suggested. The study was then extended to labile diabetes[33]. In a group of such patients who also exhibited alterations of the electroencephalogram, it was observed that the hypoglycemic incidents so frequent in labile diabetes were only in part caused by subnormal blood sugar levels. Not infrequently the blood sugar was exceedingly high during apparent hypoglycemic reactions. Such reactions could not be overcome by the administration of sugar but could be prevented by the use of anticonvulsive drugs. It was therefore concluded that electrocerebral dysfunction *per se* may produce symptoms identical with those of hypoglycemia and the term "pseudohypoglycemic reactions" was proposed for this type of reaction.

Much has been written on hypoglycemia as a factor in the production of epileptic seizures. A critical perusal of the literature discloses that even an extreme lowering of the blood sugar cannot produce either epileptic seizures[9,76,95] or an epileptic type of brain activity although it may enhance the abnormal brain wave pattern in patients with petit mal[29,30,44].

As for the status of carbohydrate metabolism in parathyroid disorders, the data are contradictory. According to some workers[80,113,118], parathyroprival tetany was accompanied by insulin sensitivity and hypoglycemia both of which were corrected by the administration of calcium. Other observers found that parathyroid extract improved carbohydrate tolerance in patients with diabetes[38] and produced a transient fall of the blood sugar in dogs[85]. Labbé et al.[74] found that calcium salts exerted a hypoglycemic effect in normal and diabetic subjects where-

as Underhill[113] reported that in rabbits administration of calcium accelerated the hyperglycemia and enhanced the glycosuria produced by adrenaline. According to Oliva[91], glucose caused a slight increase and insulin a slight decrease in serum calcium in normal and diabetic subjects. However, clinical observations indicated the usefulness of calcium in suppression of hypoglycemic convulsions after insulin even though this therapy did not influence the hypoglycemia itself[45,62,63,83]. The beneficial results obtained with calcium salts in hypoglycemia associated with hypocalcemia reported by Fabrykant[32] may of course be explained by the coexistence of these two conditions.

While no attempt is made to connect causally the 3 conditions, hypoglycemia, hypocalcemia and cerebral dysfunction, recent data on the relation between the metabolism of calcium, carbohydrate and acetylcholine indicate that the mechanism involved in the production of clinical reactions in these conditions may be similar.

Reaction Threshold. Since there is no absolute relationship between the blood sugar values and hypoglycemic reactions, Sevringhaus[103] suggested that the level at which reactions occur is an individual pattern. John[62] reported that the level may vary even in the same individual from one day to another.

The frequent occurrence of reactions at comparatively high blood sugar values raises the question of a reaction threshold. Fletcher and Campbell[40] stated that "when a reaction has already been experienced, the onset of a subsequent one is usually recognized by the patient when the blood sugar percentage falls to some point between 0.08 and 0.07 per cent." Joslin[65d] observed what he termed "false hypoglycemic reactions" to occur with blood sugar values of from 220 to 290 mg. per 100 cc. In two instances, these false reactions resembled so closely a true reaction "as to mislead a nurse and an assistant of great experience." From a study of 1000 cases of diabetes, John[63] concluded that in nearly 50% of insulin reactions, the blood sugar was high. On several occasions, he found values between 110 and 394 mg. per 100 cc. Harrop[50] reported blood sugar values between 110 and 150 mg. per 100 cc. in 4 diabetic patients with insulin reactions. It may be assumed that in such cases a certain individual susceptibility to reactions exists since it is common knowledge that the majority of diabetics do not react in this way to insulin.

An unusual sensitivity to insulin may develop as a result of inanition. This was observed in diabetics treated with starvation diets and was ascribed to glycogen deficiency. In a case reported by Joslin[65e], for instance, a reaction followed the administration of one unit of insulin and in a patient treated by Rosendahl[101] a severe reaction ensued after the administration of 2 units daily for 4 days.

In patients with hypoglycemia accompanied by hypocalcemia and electrocerebral dysfunction, Fabrykant and Pacella[32] noted the frequent occurrence of hypoglycemic symptoms in the absence of critically low blood sugar levels. Since such reactions were prevented by anticonvulsive drugs and calcium therapy, they concluded that because of cerebral dysfunction and hypocalcemia, these individuals were more susceptible to even small variations of blood sugar. In other words, it was assumed that these patients had a lowered reaction threshold; they postulated that anticonvulsive drugs and calcium therapy might have raised the threshold. In a group of labile diabetics with electrocerebral dysfunction[33] a number of reactions occurred with normal or slightly elevated blood sugar levels. Following anticonvulsive ther-

apy, the frequency and severity of such reactions were reduced even though in some instances the insulin dosage was increased. Moreover, following such therapy, the onset of reactions was less abrupt and the reactions yielded easily to small amounts of carbohydrate. It was evident that in these patients as well, the cerebral dysfunction might have decreased the reaction threshold.

In a group of patients with labile diabetes observed by one of us[16], bellergal proved effective in stabilizing the diabetic state. Since this preparation contains belladonna, ergotamine and phenobarbital, its effect might be explained by the action of its components on cerebral dysfunction. No definite statement can be made with regard to this group of patients since no electroencephalographic studies were made. Interestingly enough, in an unstable diabetic treated by Root[66b], phenobarbital decreased the sudden onset of hypoglycemic episodes.

From the foregoing, it appears that a reduced reaction threshold may be found in (a) subjects who exhibit frequent insulin reactions; these individuals behave as if they were conditioned by the frequency of reactions and are able to perceive even minor fluctuations of the blood sugar, (b) the hypoglycemia of starvation, in which condition the subjects seem to be so sensitized by the continuous dearth of glucose that minute amounts of insulin result in severe symptoms or even in fatal outcome, and (c) those subjects who in addition to spontaneous or insulin-induced hypoglycemia suffer from other conditions apt to produce symptoms resembling the hypoglycemic complex, such as hypocalcemia and electrocerebral dysfunction.

Irreversible Reactions From Hypoglycemia. Under this heading are reviewed briefly those reactions in which the basic disturbance is no longer functional but structural, i.e., reactions which result from hypoglycemic damage to the brain. A severe and prolonged state of hypoglycemia may produce anatomic lesions in the central nervous system such as edema of the brain, cerebral and meningeal hemorrhages, necrosis of the cortex characterized by degeneration and disintegration of ganglion cells, and swelling of the glia and axis cylinders[6,39,64,66c,75,119c]. It is obvious that such lesions may cause profound alterations in brain function accompanied by various clinical manifestations. Such clinical reactions, however, need not be correlated with the glucose concentration in the blood since they are not in the nature of hypoglycemic but rather post-hypoglycemic phenomena related to brain changes which persist even after hypoglycemia and cerebral glycopenia have been corrected.

The injury to the brain from hypoglycemia may be of short duration and reversible[98] or it may be irreversible. Thus, the hypoglycemic state and unconsciousness may persist for days and be followed by slow recovery or there may be residual and permanent abnormalities such as epilepsy, mental deterioration and idiocy[2,4,64,69,119d]. In some instances, the patients fail to survive the attack, and death may occur 3 to 23 days after the insulin has been discontinued and the blood sugar elevated to normal or hyperglycemic values[64,75,100]. Such fatal episodes may develop in hyperinsulinism as well as in hypoglycemia produced with both the unmodified and the slow acting insulins. In 1922 Woodyatt[121] reported the case of a patient with diabetes and inanition. The urine was sugar-free on admission. The diet was increased and a calculated dose of insulin was given. Hypoglycemic shock resulted during which the blood sugar was found to be too low to be determined.

The administration of sugar was followed by a rise of the blood sugar to hyperglycemic values with the production of glycosuria but the patient died without regaining consciousness.

In hypoglycemia produced by an overdose of protamine-zinc insulin, symptoms may be absent for hours and fatal convulsions from brain damage may develop after the blood sugar has been raised to normal or even hyperglycemic levels. Bollman[11] made dogs hypoglycemic for 50 to 60 hours with protamine-zinc insulin. When sugar was administered to restore the blood sugar, the animals went into fatal convulsions and autopsy revealed a large number of petechial hemorrhages in the brain. Sherrill and MacKay[104] also produced a stuporous hypoglycemia in dogs with protamine-zinc insulin associated with a fall of the blood sugar to between 20 and 30 mg. per 100 cc. for 24 to 48 hours. Here again, elevating the blood sugar to normal by the administration of sugar failed to protect the animals from death.

Reactions which develop as a result of brain damage from severe hypoglycemia may of course show great similarity to reactions in which there is no brain damage. While these reactions are initiated by critically low blood sugar values, they cannot be regarded as true hypoglycemic episodes, since they are produced by structural and not functional changes in the brain. The term "post-hypoglycemic encephalopathy" suggested by Jones[64] seems more appropriate to designate this type of reaction.

Role of Epinephrine in Insulin Reactions. As mentioned earlier, in 1923 Boothby and Wilder[12], suggested that insulin reactions were due to a secondary release of epinephrine since the symptoms noted during hypoglycemia were not dissimilar to those observed after the administration of epinephrine. Soon thereafter, Riddle et al.[97] lent support to this concept by demonstrating that repeated injections of insulin caused hypertrophy of the adrenal glands. Further evidence strengthening this concept was provided by the work of Cannon[19], Houssay[61] and Macleod[78] on the role of the sympathetic-adrenal system in the mobilization of endogenous glucose in response to subnormal blood sugar values.

In 1901, Blum[10] demonstrated that epinephrine raised the blood sugar by mobilizing liver glycogen. This observation has been confirmed repeatedly. Later, the Coris and other workers[22,23,24,25] showed that epinephrine hyperglycemia resulted rather from decreased utilization of the blood sugar in peripheral tissues. The observation that insulin accelerated utilization of blood sugar and inhibited hepatic glycogenolysis produced by epinephrine established the antagonism between these two hormones[24,25].

Much experimental work accrued to fortify this concept of insulin-epinephrine antagonism. Britton et al.[15] showed that animals deprived of their adrenal function were hypersusceptible to the hypoglycemic effect of insulin. Crandall and Cherry[26] observed that adrenalectomized or adrenal denervated dogs went into shock as soon as one hour after the injection of 15 units of insulin and they postulated that the secretion of epinephrine is stimulated when the blood sugar level drops to a point between 50 and 60 mg. per 100 cc. Brandt and Katz[13] demonstrated the presence of vasoconstrictor substances, presumably epinephrine, in human blood during reactions induced by the intravenous administration of 20 to 30 units of insulin. In this regard, it is interesting to note that in patients undergoing insulin shock therapy, Heilbrunn and Liebert[53] found little or no vasoconstrictor substances in the blood of those readily

going into insulin shock. In those in whom insulin produced mild symptoms such as drowsiness and perspiration, there was a sharp rise in vasoconstrictor elements in the blood which they presumed to be epinephrine. In an indirect fashion, Kugelmann[72] attempted to show an increased production of epinephrine during insulin hypoglycemia; he injected ergotamine with insulin into 10 patients and obtained hypoglycemia without the circulatory signs in 4 of these. These patients, however, exhibited tiredness, weakness and hunger. Even if one assumes the validity of such observations, it is obvious that no correlation has been shown to exist between epinephrine secretion and hypoglycemic reactions.

The homeostatic regulation of the blood sugar is undoubtedly under the control of the endocrine system. However, the part played by the adrenal medulla is probably insignificant. The experiments quoted above indicating the increased sensitivity of the adrenalectomized animal to insulin must take into account the fact that the adrenal cortex is simultaneously eliminated. Thus, Swann and Fitzgerald[108] showed that in rats the removal of the adrenal medulla increased insulin sensitivity only twice, whereas removal of both parts of the adrenal increased it 24 times. Hence, the adrenal cortex appears far more intimately involved in insulin antagonism than is the medulla.

The role of the endocrines in the regulation of the blood sugar has been well stated by Soskin[107]. This author maintains that the output of sugar by the liver is to a certain extent controlled by the sugar present in the hepatic cells even in the absence of any possible endocrine adjustment. In addition to this intrinsic hepatic mechanism and its endocrine regulations (anterior pituitary, thyroid and adrenal cortex) there are also certain emergency mechanisms mediated by the central nervous system and the adrenal medulla.

In the present paper, the importance of the central nervous system in the production of the clinical hypoglycemic state has been stressed. The homeostatic regulation of the blood sugar during emergency situations may represent an attempt of the adrenal medulla to correct the subnormal blood sugar concentration. Whether this process will be effective in abolishing the clinical symptomatology will depend primarily on the degree to which cerebral function has been depressed and on the ability of the brain to respond to the increase in blood sugar.

Role of Potassium Deficiency in the Hypoglycemic Reaction. In reactions from an overdose of insulin, some of the hypoglycemic manifestations may be related to potassium depletion. A decrease in serum potassium after the administration of insulin was reported soon after the discovery of insulin by Harrop and Benedict[51] and by Briggs et al.[14]. In a case of spontaneous hypoglycemia, McQuarrie et al.[84] observed a rise in blood sugar with partial relief of symptoms following administration of potassium chloride. They felt that the use of potassium salts may be helpful in the prevention of insulin reactions in diabetes. However, the clinical significance of hypopotassemia in diabetes remained unrecognized until the recent report of Holler[58]. From Holler's observations and those which followed his paper[41,82,89], the syndrome of potassium deficiency after insulin may be pictured as consisting of muscular weakness, extreme respiratory distress, increased pulse pressure, heart dilation, cardiac arrhythmia, rise in venous pressure and a group of characteristic changes in the electrocardiogram. In the past, some of these symptoms were ascribed to the depression of the blood sugar but recent evidence

unquestionably supports the view that they result from potassium deficiency. These symptoms may persist even though the blood sugar has been restored to normal but yield promptly to the administration of potassium salts orally or parenterally.

The mechanism underlying the decline in serum potassium after insulin is still a matter of discussion. In diabetic acidosis and coma, potassium may be lost in the urine in excess as a result of tissue breakdown, glycosuria, diuresis, etc.[5,41]. When insulin is given to combat the acidosis, a shift of potassium from the extracellular fluids into the cells and liver occurs. This migration of potassium may be correlated with the effect of insulin on the oxidation of sugar, formation of intermediary carbohydrate-phosphate compounds[51], glycogenesis[37] and the resynthesis of tissue proteins[41] since potassium ions are required in all these processes. Furthermore, the drop in serum potassium during the period of recovery from diabetic acidosis may be due in part to a number of other factors such as the use of large amounts of fluids, saline and in some instances bicarbonate and glucose. All workers, however, agree that insulin undoubtedly plays an important part in lowering the serum potassium even though this effect may not be a direct one. Frenkel et al.[41], for instance, pointed to the compensatory secretion of epinephrine or some adrenocortical hormones as possible factors.

The clinical manifestations of potassium deficiency have been appreciated from earlier work in muscular paralysis, familial periodic paralysis, infantile diarrhea and chronic nephritis. Low potassium concentrations are thought to interfere with muscle metabolism and contraction[109]. However, just how potassium deficiency affects muscle metabolism has not been elucidated. It is conceivable that this phenomenon involves some disturbance in the metabolism of acetylcholine. Mann[81] and Feldberg[36] observed that potassium ions increased the synthesis of acetylcholine and facilitated the release of this substance. Nachmansohn and Machado[88] showed that potassium was essential for the activation of the acetylcholine synthesizing enzyme, choline acetylase. Since acetylcholine is necessary for the conduction of nerve impulses and their transmission across the synapse and myoneural junction[17,87], it is conceivable that potassium deficiency by inhibiting the synthesis as well as the release and removal of acetylcholine may result in muscular weakness and paralysis.

In most cases of diabetic coma, the potassium deficiency syndrome is absent[41]. Furthermore, the syndrome may account for only a small proportion of symptoms observed in severe or fatal hypoglycemia. Thus, potassium deficiency seems to be of only secondary importance in the production of the less severe hypoglycemic reaction. In this connection, it is of interest to note that the symptoms of potassium deficiency bear some similarity to those described by Himwich[54] as occurring in the last phases of hypoglycemia. Since at this point, neither glucose nor oxygen is any longer effective, Himwich feels that soon after the myelencephalic stage has developed, hypoglycemia becomes irreversible. However, it is conceivable that some hypoglycemic reactions considered heretofore to be irreversible may be corrected by the use of potassium salts. Consequently, irreversible reactions would be represented mainly by those in which actual brain lesions from hypoglycemia render all therapy ineffective.

Integration of Factors Involved in the Mechanism of the Hypoglycemic Reaction. The recognition that a sub-

normal blood sugar was accompanied by a group of characteristic symptoms proved fruitful in laying down the foundation for our understanding of the hypoglycemic reaction. As a result of this concept, however, the idea was entrenched that the symptoms accompanying hypoglycemia must always be related somehow to an excess of insulin or to a decrease of the blood sugar. The occasional though not infrequent demonstration of discrepancies between the clinical and laboratory findings in hypoglycemia was at first disregarded. This was probably due to the fact that observers failed to project the implications of such observations into the sphere of general functional disturbances. The recognition that glucose was the main nutritive substrate of the brain and that an inadequate supply of this sugar by producing secondary brain anoxia might account for the clinical picture of hypoglycemia was a great step forward. Yet, it was clear that the mere lowering of the brain sugar, whether reflected in the systemic blood or not, could not produce hypoglycemic symptoms and that the only way in which such nutritional deficiency could evoke a reaction was by inducing alterations in the function of the brain cell. It was also clear that cellular function of the brain could not be explained solely on the basis of two biochemical events, namely, the utilization of carbohydrate and the uptake of oxygen. Other substances, e.g., calcium, were also essential and it was obvious that disturbances in the metabolism of these substances might also disturb profoundly the enzymatic reactions in the neuronal cell. Similarly, cerebral anoxia *per se*, e.g., carotid sinus syndrome, heart disease[31] and cerebral arteriosclerosis, might by virtue of its interference with brain function produce the clinical syndrome. Moreover, it should be recognized that function is not synonymous with metabolism and that the function of the brain may be disturbed independently of nutritional or metabolic factors. Such considerations suggest that the clinical symptomatology generally recognized as the hypoglycemic reaction is (a) the expression of a disturbance in brain function, (b) that this disturbance is revealed in the distorted cerebral electroactivity and (c) that the disturbed brain function is the common denominator of all such reactions.

The interpretation of the hypoglycemic reaction on this broader background appears to be of practical importance. The recognition that a similar clinical end result may be obtained in a variety of ways might be helpful in distinguishing reactions due to factors other than hypoglycemia. It may also be helpful in understanding that when several such factors are operative in the same individual, the reaction threshold may become reduced and the character and the intensity of reactions may be greatly modified. Lastly, the concept is also important because of its therapeutic implications. It may enable the clinician to treat patients with spontaneous hypoglycemia and labile diabetes more adequately than heretofore.

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NEUROLOGY AND PSYCHIATRY

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PSYCHOTHERAPY: AN ORIENTATION FOR NON-PSYCHIATRISTS

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Addressed to non-psychiatrists, this paper seeks to review in summary the more practical aspects of psychotherapy as they presently apply to the private practice of medicine and surgery. Admittedly fraught with sins of oversimplification, unwarranted generalization, and omissions, such an approach is vulnerable to attack by both psychiatrist and organicist. If, however, orientation in a confused terrain is furthered, the overworked plea of expediency may be justified.

Too much popular emphasis has plagued us *via* printer's ink, Hollywood celluloid, and radio scripts to make it necessary for this writer to demonstrate the ubiquity of psychopathology in our culture. The prevalence, at least, of psychopathology is evident. But we hear much, too, of "atomic" fission and its potential military application to abbreviate our life expectancies. Clearly, one may recognize the *existence* of a lion one has by the tail—yet remain quite unprepared to let go with safety. Private practitioners repeatedly find themselves in such an unsolicited and unapplauded role; *viz.*, being confronted by a patient whose illness may be far more readily *identified* as psychogenic than *treated* as such—either directly or by referral. Among the barriers to optimum management may be arrayed a distrust or unfamiliarity on the part of the physician concerning psychotherapy, the practical (geographic and economic) difficulties of referral to a psychiatrist when indicated, and insufficient insight on the part of the patient into the psychogenic nature of his illness.

TO REFER OR NOT TO REFER? Studying his patient with predominantly "functional" symptoms, the physician may logically ask himself, "Shall I best serve this patient by symptomatic therapy and common sense advice, or by referral to a psychiatrist?"

One may say that the decision rests upon "clinical judgment" in reference to the specific case. True, but we use the phrase often to account for intuitive selection. Intuitive judgment, born of clinical experience, plays at least as significant a role in therapeutic management as it does in the diagnosis and the *art* of medicine as a whole. But if we affect a scientific basis for what we do, intuition—however valuable—must continuously lend itself to conversion into rational principles as our knowledge increases. Principles, not intuition, lend themselves to objectification, revision, pedagogy, and broadening practical application.

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Or one may decide to refer to the psychiatrist all patients with handicapping psychiatric symptomatology, at least all such patients who fail to respond promptly to simple reassurance and palliative medication. Were referral economically and geographically possible in each case, were there enough psychiatrists to go around, and were one's patients willing to be placed at the tender mercies of the psychiatrist—even then such a policy would be wasteful of the patient's resources and the physician's training. Not all these patients are curable, nor is specialty psychiatric care necessarily the most successful, broadly considered.

Denker[8], for example, concluded from a survey of 500 disability insurance claims for psychoneurosis treated with superficial therapy by general practitioners, that the duration of disability and percentage of improvement or cures showed "no significant difference in the therapeutic success obtained by practitioners, psychiatrists, or psychoanalysts" (comparing his statistics with those reported in the literature by specialists). He felt from his study "that most psychoneuroses, as do many other diseases in medicine, run a self-limited course, and that the 'time factor' is of the greatest importance. The common sense and judgment required in intelligent treatment of this condition can be as effectively provided by the capable general practitioner as by the psychiatrist."*

"Finally," as Groom[14] remarks, "there is something to be said for (psychotherapy's) downright interest, for a patient's mind can be as interesting as his colon."

The following considerations, though mutually interrelated, are discussed separately for convenience in attempting to objectify the often more or less intuitive criteria by which one may decide for or against referral of his patient to a psychiatrist:

1. **Diagnosis.** Certain nosologic entities seem by their nature to demand specialized attention; *i.e.*, are otherwise unapproachable or too hazardous to justify palliation or brief psychotherapy by the non-psychiatrist. Psychoses, acute or chronic, are of this category because they usually require (a) potential closed ward security for protection against irresponsible injury to self and others, and (b) intensive treatment at minimum risk to render the personality accessible to psychotherapy (*e.g.*, electro-convulsive therapy, insulin shock therapy, hydrotherapy). These include disabling schizophrenia, or schizophrenia with active delusional systems; major deviations of mood (depression, elation, cyclothymia). Organic psychoses (*e.g.*, toxic deliria, general paresis, senile dementia) when severe usually require closed ward psychiatric management for safety and maximum benefit. Psychoneuroses, when (a) severe or acutely disabling (*e.g.*, reactive depression, panic, disorganizing anxiety reactions, certain hysterias), or (b) too chronic and inaccessible for conservative management (*e.g.*, obsessive-compulsive-ruminative neuroses, chronic invalidism, psychogenic asthma) may require referral.

Conversely, the non-psychiatrist has distinct advantages of rapport and flexibility in symptomatic management of many acute hysterias, mild and moderate anxiety states, and certain of the psychosomatic disorders (*e.g.*, peptic ulcer, essential arterial hypertension, "mucous" and "spastic colon" syndromes). He sees them earlier in their genesis, in the context of situational dissatisfactions and still blissfully free

*Despite Dr. Denker's careful defense of the acknowledged margin of error in such a study, this writer finds it hard to accept the validity of his conclusions from comparisons among widely variant sources and clinical criteria, especially in view of the inevitable automatic selection of cases for (a) insured disability, (b) specialty psychiatric management, and (c) pyschoanalysis. The data are nevertheless regarded as of sound illustrative import.

of the social stigma of being "mental."

2. **Severity.** Generally speaking, the more severe the personality distortion and functional disability, the more pressing is the demand for intensive treatment and rapid resolution of symptoms. The hazard of self-injury or impulsive action increases (within limits) with severity, as does the risk of personality rut-formation, hopelessness, regression, social and therapeutic exile.

3. **Prognosis.** Estimating prognosis in psychiatric illnesses propounds one of the most unsatisfactory and elusive tasks in all of medicine, depending as it does upon multiple and interrelated variables—not only existent within the patient and inherent in the illness, but also at the mercy of a changing situational milieu. But however non-committal the physician may try to be in discussions with patient and relatives, he must consider at least privately the possibility and practicality of effective treatment, and usually must give the patient and others some rough prediction on which to plan. Other factors conforming, he may elect to retain for corrective treatment those patients with reasonably good prognosis, and those with such poor prognosis that only supportive and palliative care are indicated. In the latter event, of course, he is often wise to seek a psychiatrist's confirmation, if only to share the dissatisfaction arising when partial or no symptomatic relief can be obtained in management. Those patients with only fair or doubtful prognosis, or good prognosis only with intensive psychotherapy, are best handled by referral for specialized treatment.

A review of the following factors can be of some assistance in prognostication—within considerable margins of error:

A. **History of past performance:**
   1. Favorable:
      a. Average or better school work, social and marital adjustments preceding the onset of the illness.
      b. Consistency in effort, goals, standards—but not to the extent of rigidity or perfectionism.
      c. Failures and illnesses only in relation to *severe* stress (*e.g.* the soldier who broke down in severe and sustained combat, as opposed to the inductee who developed analogous symptoms during basic training).
   2. Unfavorable:
      a. Early and/or repeated emotional illnesses during life, in response to minimal or average stress.
      b. "Neuropathic" traits in childhood, especially if sustained; evidence of developmental anxiety during formative years (*e.g.* enuresis, excessive nailbiting, tantrums, phobias).
      c. Impulsivity in school, work, social behavior.
      d. Insidiously developing psychopathology.

B. **Current personality factors:**
   1. Favorable:
      a. Evidence of basic maturity.
      b. Strong therapeutic motivation (anxiety, aggressiveness, future goals).
      c. Rapport with physician.
      d. Insight (acceptance, at least, of psychologic mechanisms related to symptoms or coincident thereto).
      e. Average or better intelligence.
      f. Broad fund of experience and interest.

2. Unfavorable:
   a. Marked immaturity.
   b. Apathy, indifference to illness, self-centeredness.
   c. Delusional content; unrealistic and autistic thinking.
   d. Preoccupation with organic symptoms.
   e. Narrowed intelligence, interest, and experience.
   f. Evidence of "neuropathic" traits (nailbiting, tics, stutter, etc.).
   g. Incongruous affect or unaffected biologic rhythms in contrast to severe symptomatology.

C. **Situational factors:** Prognosis proportionate to:
   1. Capacity for insight, modification on part of relatives, associates.
   2. Alterability of anxiety-producing stress and dissatisfactions (economic, interpersonal, etc.).

Know thyself. Psychotherapy presupposes on the part of the physician a working awareness of psychodynamics, acquired intuitively, experientially, and/or through specialized training. A working knowledge, too, of psychotherapeutic tools is prerequisite to flexible and efficient utilization of the potential opportunities for treatment. But equally significant are certain personality qualities of the physician himself. Psychotherapy, almost by definition being "relationship" therapy of patient by the doctor, the temperamental attributes of the therapist become powerful assets or liabilities in treatment—awareness of which in reference to the patient at hand may well determine whether the patient should be retained for treatment or referred elsewhere.

Although addressed to psychiatrists, the remarks attributed to Bartemeier[4] might well be applied to all physicians who include psychotherapy in their practice: "It is not given to all men by virtue of their childhood, adolescent and adult experiences, even though they have the necessary scientific background, intelligence and ordinary social gifts, to have the capacity for empathy. Successful psychotherapy presupposes . . . a certain feeling of conservative optimism, an ability to put one's heart into a problem yet have the courage to say so when a problem is beyond one's capacities. The psychiatrist must not have too many conflicts of his own. He must make sure that he is straightened out with himself before he tries to help other people." A deft manipulator of the scalpel, for example, may or may not be equally facile in the manipulation of his own personality for the treatment of others.

A comfortable recognition of the time factor in psychotherapeutic management is of the greatest practical importance (Billings,[5] p. 224). One must be willing to allow interview time of one-half to one hour per session when indicated, often over periods of weeks or months. One must learn to be content with gradual and partial successes, the pace and degree of which are almost as little within the voluntary control of the patient or the doctor as is the constitutional resistance which effects a remission of pulmonary tuberculosis. Rogers,[24] writing of his management of tension states in general practice, counsels that the physician must have an attitude of "'objective noncritical listening,' in which the patient can discover for himself what his emotional conflicts are. The patient must feel free to work out his conflicts and solutions for himself." Rogers admits that this "is time consuming, but it is not all to be done at once. Were

the shortness of breath and palpitation due to pernicious anemia the illness would not be diagnosed or cured at one sitting."

In other words, he who essays practicing rational psychotherapy must recognize his own attitudes and personality structure as a part of the functioning therapeutic situation; notably, the physician's own sensitivities, tolerance, willingness to spend time, and reasonable patience in playing a passive listening role when required. On the other hand, it is not suggested that successful psychotherapy requires a physician of unsullied personality (provided he knows and allows for his quirks), unlimited time and inanimate mien. It is not meant to imply that the majority of cases require months of therapy, although a willingness to spend this long if required is desirable. Actually, the average acute anxiety or tension state which one sees in general practice requires about three or four interviews at the most for immediate relief.

Nor should the non-psychiatrist infer too exaggerated a concern about the "risks" of his performing occasional psychiatric management. It is the writer's opinion that the alleged "risks" of psychotherapy by non-psychiatrists are grossly overemphasized, provided the therapist is at least more of a listener than a judge, and is content to leave in the hands of the patient the initiative for probing into painful areas. Panic and acute psychotic reactions *do* result from heavy-handed direction or from premature exposure by the therapist of conflict-ridden areas (no matter how correct the interpretation); but even this is infrequent and can usually be averted by the timely recognition of stormy weather and prompt reversion to palliative reassurance or "non-directive" aeration of the disturbing content.

The common-sense avoidance of bulldozer approaches in psychiatry is no more mysterious than it is in orthopedics. One does not test the initial movement of a partially ankylosed joint with active flexion—the patient is encouraged to find the limits of his own endurance, even cautioned to stop short of the absolute limits. Giving his qualified endorsement to a passive therapeutic attitude, Whitehorn[26] points out that the psychiatrist is thereby restrained from the too hasty and meddlesome projection of his own prejudices and presuppositions into the patient, and is more ready to grant the patient spontaneity and opportunity for expression: "Many of the harmful errors in 'over-active' therapy arise from a domineering attitude and from the uneasy and artificial necessity of playing Jehovah to the patient." "Yet much foolish delay and pernicious distortion of issues is also perpetrated in the name of passivity." Whitehorn adds that it is his "strong impression that the development of the therapist's most effective style of 'passivity' comes through much experience . . . because many patients, bit by bit, thoroughly convince the therapist of their own contribution to therapy and thus cultivate in him a very genuine respect for them."

Which psychiatrist? Members of the medical profession are prone to regard archly the irrational bases upon which laymen choose their physicians (not to mention their cultists). Yet our own referrals to specialist-colleagues are frequently only slightly more considered—based often upon the outcome of previous, dissimilar referrals; upon habitual contact with particular consultants; and sometimes solely upon their technical training and prestige. The choice of a psychiatrist—at least in larger communities where a choice is possible—brings into bold relief the importance of selecting the specialist to fit the patient. Successful psychotherapy may well be more dependent upon the aptness of the specialist's

personality, interest, and approach than upon his formal training.

As in any field where progress is occurring and where many questions must yet be answered on the basis of opinion, psychiatry is practiced by men who are united generally upon a broad base of theory, but who differ widely in its practical applications (*e.g.*, in therapy). Happily, at this writing, the schisms between mutually repellent "schools" of psychotherapy are progressively narrowing, as evidenced by Alexander's and French's[3] pragmatic adaptations of psychoanalysis to brief therapy, and by Masserman's[21] efforts to integrate inductively Myerian (psychobiologic) and Freudian (psychoanalytic) principles into a "Biodynamic theory of behavior." But even were the academic differences universally resolved, significant differences of interest, facility, and temperament would remain among individual psychotherapists. The day has long since passed when psychiatrists were exclusively found (practicing) within the walls of mental institutions. Specialty board certification in psychiatry endorses men whose proficiency varies from pediatric psychiatry to schizophrenia. One man may achieve brilliant results in the treatment of psychoses with insulin and electro-convulsive treatment, yet lack the patience and personality qualities for success in the treatment of psychoneuroses—and *vice versa*. To the general practitioner (who must survey the entire gamut of medicine) these nuances and sub-specialties may well seem hypothetical and unnecessary—annoyed, he may attempt to find one psychiatrist with universal aptitudes, or else insist that it is the psychiatrist's job to adapt himself to the patient ("After all, psychiatrists tell their patients how to adapt"). Nevertheless where choices exist, both extremes are unrealistic and as wasteful as referring a patient with brain tumor to a competent chest surgeon.

The sub-specialty of psychoanalysis requires particular mention because of its profound theoretical influence upon all psychotherapy, and because of its rather specific applicability—despite the multitude of popular misconceptions about Freudian methodology and rationale. Inductive and "microscopic" in its approach to the study of personality, classical psychoanalysis is the most scientific, least practicable psychotherapeutic discipline. To its theory and research we owe a great share of our concepts of the structure of personality, the psychodynamics of illness and health, and the rationale of psychotherapy. But "standard" psychoanalysis as generally practiced is unfortunately an unwieldy implement, beyond the reach of all but a minute fraction of psychiatric patients because of (a) the cost (rarely less than $2000 annually), (b) the time (roughly, 18 months to 3 years; one-hour interviews daily, weekly, occasionally monthly), (c) the shortage of qualified psychoanalysts, and (d) often (appropriately) strict criteria of "treatability." Its application classically is analogous to radical surgery—justified in private practice when conservative therapy is ineffectual, but not when prognosis is hopeless. It has been estimated that less than 10% of psychiatrists' patients merit trial analysis, and of these only a few can continue (*i.e.*, have the requisite personality requirements and the practical opportunity to do so).

Still in experimental stage, and apparently actively opposed by a majority of psychoanalysts, are efforts to modify the classical Freudian discipline by planned, abbreviated therapy in which the therapist plays a more active and directive role[3,21]. Alexander[3] points (pp. 5-6) the direction of this development when he urges a "plan of treatment" and the "*conscious use of various techniques in a flexible manner*, shifting tactics to fit the particular needs of the

moment . . . using not only the method of free association but interviews of a more direct character, manipulating the frequency of the interviews, giving directives to the patient concerning his daily life . . . and making use of real-life experiences as an integral part of the therapy."

When compelled to select a psychiatrist in a locale where he has no personal contact, the referring physician must rely upon directory information; *viz.*, directories of local, state, and national medical associations; directories of specialists (diplomates of the American Board of Psychiatry and Neurology; affiliates of the American Psychiatric Association, and of regional and subspecialty associations). While a poor substitute for direct acquaintance, a knowledge of the consultant's training, academic affiliations, and emphasis in practice are of aid. Certification by the Board of Psychiatry and Neurology (in psychiatry or both) or membership in the American Psychoanalytic Society is evidence of both didactic and training requirements having been fulfilled in those fields.

Economics of psychiatry. Something must be said in defence of the alleged "expensiveness" of psychiatric treatment—even at the risk of gross overgeneralization from personal observations. Based on the total cost per patient-illness, it is indeed expensive in long-term cases—a crushing blow to the patient who is in even moderate circumstances. Still more overwhelming is the burden when disability and hospitalization supervene; worse if the patient has already run the gauntlet of diagnosis and therapy "by exclusion" with psychiatric intervention deferred as a last, desperate resort.

But a glance at tabulations of comparative incomes among physicians discloses neuropsychiatry as falling well below the mean, usually at or near the lowest income brackets of the profession—consistently below that of general practitioners, regardless of time in training. The cause of this seeming paradox (patient expense *vs.* doctor's income) is, of course, *time* and *volume* of patients. Only rarely can a psychotherapeutic interview be effective in less than one-half hour, and more usually an hour is required, with longer periods required for special examinations. Thus the psychiatrist's case load rapidly reaches a ceiling, his time saturated with a third or less the average number of daily patients, and his total cases per year necessarily limited because of the chronicity and spacing of treatment for each. Another economically significant characteristic is that psychotherapy can rarely be delegated—at least in private practice—to an assistant (associate, psychologist, social worker) or to a nurse. This is in direct contrast to the manipulative and pharmacologic ancillaries helpful in organic therapeutics.

Fees for psychotherapy in certain metropolitan centers have been observed by the writer to approximate $15 to $25 per treatment hour for pay-patients, with the lower figure rather consistently maintained for those in middle-income brackets. On the basis of *treatment time*, it is evident that the fees for psychiatric care are quite comparable to the $3 to $5 which a non-psychiatric patient would expect to pay for an ordinary office visit, as one of the several patients seen in that hour by the doctor. Fees for psychiatric management in hospital are less standardized, but it is doubtful that the psychiatrist's share exceeds that of the internist, and very likely falls well below the hospital fees of an active surgical practice.

These justifications, naturally, do not ameliorate the problem of economics for the psychiatric patient, who must nevertheless subsidize a greater proportion of the doctor's time than if he were afflicted with pneumonia or

a fractured femur. Their recognition, however, can orient the referring physician for practical advice to his patient, and can help the patient to understand the realities of private psychotherapy—thereby protecting rapport as well as public relations for private medicine as a whole. For patients of restricted and lower income brackets—even though capable of ordinary private medical care—it is usually more constructive and foresighted to encourage acceptance of treatment at tax-supported psychiatric facilities (mental hygiene clinics, child guidance clinics, teaching hospitals, state facilities) where available, than to press private psychotherapy in disregard of the additional stress which is ultimately created for the patient financially.

THE NATURE AND AIMS OF PSYCHOTHERAPY. Psychotherapy, as connoted in this discussion, may be defined as *any therapeutic effort to improve by psychologic means the patient's adaptation to reality.* Thus, *therapeutic efforts* can range from direct personality training to the fostering of healthier factors in the patient's life-situation (*e.g.*, attempts to alter the attitudes of relatives, to aid in the solution of environmental problems. *Psychologic means,* broadly interpreted, implies major (but not exclusive) reliance upon personality function as an instrument of treatment, as opposed to primarily somatic procedures; operating through the influence of the therapist in his relationship with the patient and the latter's milieu. In *improving adaptation to reality* one must measure progress not only by more efficient and constructive behavior, but also by the reward of a fair share of gratification. *Reality,* of course, includes psychologic, biologic, environmental, and inter-personal factors (Alexander and French,[3] pp. 8, 11, 14, 18, viii).

Prerequisite to efficiency is the abandonment of neurotic goals[26], and the achievement of that tenuous and relative state of "maturity." Levine[18] itemizes (p. 286) some criteria which are helpful in measuring the degree of *emotional maturity* (especially in contrast to neurotic character-formation):

(a) ability to be guided by reality rather than by fears.

(b) use of long-term values.

(c) grown up conscience.

(d) independence.

(e) capacity to "love" someone else, but with an enlightened self-interest.

(f) a reasonable dependence.

(g) a reasonable aggressiveness.

(h) healthy defense-mechanisms.

(i) good sexual-adjustment with acceptance of own gender.

(j) good work-adjustment.

Elimination of undesirable attitudes and symptoms, of unrealistic goals and immature behavior must not, however, be assumed as the sole objective of psychotherapy—any more than the excision of diseased organs can be regarded as a sufficient guarantee of health. The psychiatrically ill patient is, in fact, in desperate need of replacements when his pathologic symptoms have been denied him or rendered no longer tenable. Frank,[12] for example, insists that if neurotic behavior is conceived as adaptive to situations perceived as threatening, into which the individual has no insight, then removal of the neurotic symptoms is of little value so long as the personality remains "saddled with the original conflict." If psychotherapy can not *replace* the neurotic symptoms with healthier patterns of behavior through reorganization of the personality or its function, we must then be content to minimize the handicap of functional symptoms—which symptoms, though pathologic, at least constitute a working mechanism of adaptation. It is both harmful and futile to insist righteously upon the removal of all protective symptoms unless there is prospect of the patient's

accepting a healthier alternative.

In addition to the realistic acceptance of *relative* success in psychotherapy (consistent with the patient's ability and practicality), it is useful to separate treatment tasks into what Whitehorn[26] categorizes as "major psychotherapy" (procedures directed toward overcoming the repetitive tendency of psychoses and severe neuroses), and "minor psychotherapy" ("procedures appropriate to the brief psychiatric episodes in which the patient's natural resources suffice for recovery with only minimal assistance"). This done, one is better prepared to select those particular therapeutic devices most appropriate; a number of which are reviewed below.

TOOLS OF PSYCHOTHERAPY. 1. **Radical techniques,** not applicable to non-psychiatrists' use. Certain techniques for intensive therapy are not feasibly adapted to use by non-psychiatrists, because of the hazards involved, the special training required for effective utilization, the need for special facilities and available psychiatric hospitalization in the event of acute psychotic reactions, and the time factor. They are reviewed here briefly for orientation:

(a) **"Shock" therapies.** Although not strictly psychotherapeutic in themselves, these procedures facilitate psychotherapy, and without the latter are often ineffective or of transient value. Their neurophysiologic mode of action is unknown, but they may be thought of functionally as useful in "fragmenting" certain fixed and pathologic associational patterns of thinking and emotional behavior, through the intervention of violent cortical excitation and unconsciousness. A secondary, purely psychologic, effect may be of significance; *viz.*, the satisfaction of a need for punishment in expiation of unconscious guilt.

Electro-convulsive therapy has displaced metrazol-induced convulsions because of the former's greater safety, convenience, and comfort; but carries about the mortality of a general anesthetic in addition to the occasional morbidity of long-bone fractures, mild vertebral compressions, muscular and ligamentous sprains. Curare can lessen the risk of fractures and dislocations in cases of known skeletal weakness, but adds the hazards of myocardial weakness and respiratory failure.[16] (Kalinowski and Hoch,[16] p. 150). Preliminary sodium pentothal narcosis has greatly reduced the anticipatory anxiety of treatment and the annoying confusion of recovery. Currently experimental use of uni-directional current and asymmetric placement of head electrodes gives promise of reducing the violence of initial convulsions, and the secondary confusion, respectively. Electro-convulsive therapy is indicated in functional (non-organic) psychoses; it is more reliable for the affective (mood deviation) psychoses and acute schizophrenic reactions than for the more chronic, insidiously developing psychoses (*e.g.*, chronic paranoid and hebephrenic schizophrenias). Its use in psychoneuroses and immaturity reactions is generally condemned, being justified probably only when these syndromes are so severe as to present a stage of rut-formation approximating psychotic deviation, thus rendering the patient otherwise inaccessible to psychotherapy.

"Pure" affective (mood) disorders require usually ten or less electro-convulsions in all (usual frequency: 3 to 2 per week), whereas those disorders which include topical (thinking) disturbances usually require from ten to twenty treatments. In those rare psychoneurotic disorders which justify electro-convulsive therapy, usually six or fewer seizures will produce what

benefits are to be obtained. The actual number of treatments required irrespective of diagnosis, however, is determined by the cumulative effect upon the patient's mood, behavior, and insight; but rarely are more than 20 in a series justified. As improvement occurs most psychiatrists prefer to space the treatments at increasing intervals (from 3 to 2 or 1 per week), discontinuing entirely for observation when symptoms have largely cleared. By the time a patient has had no relapse over a period of 2 or 3 weeks without treatment, electro-convulsive therapy can be discontinued altogether, a late relapse then being unlikely. The confusion and amnesia for recent memories, which are a cumulative side-effect of electro-convulsions, begin to clear as treatments are spaced more than 3 days apart, and are as a rule dissipated within 3 weeks of the last treatment. Treatments may be given in hospital either on an in-patient or out-patient basis, depending upon the adequacy of home care, the patient's cooperativeness, and the degree of confusion and mood-swings attending treatment. During the course of electro-convulsive treatment, intensive psychotherapy is feasible only early in the series and subsequent to about one week after completion, because of the retention defect described.

Insulin shock therapy (in contrast to tonic or sub-shock insulin) has been used almost exclusively in schizophrenic disorders, particularly those of more insidious development, refractory to electro-convulsive treatment, and characterized by fixed delusional or hallucinatory systems. Its use alone has become less common with the development of electro-convulsive therapy, but is still of value in combination with the latter for refractory cases of poor prognosis. Deep insulin therapy has the disadvantages of somewhat greater hazard (mortality and morbidity), requiring prolonged hospitalization and expert nursing care, and considerably more conscious discomfort than electro-convulsive treatment. The frequency and duration of treatment vary widely, but often a total of 40 to 80 comas (1 daily for 6 mornings weekly) with electro-convulsions interspersed during the initial weeks (2 to 3 times weekly at the height of coma) are considered desirable.

(b) **Continuous sleep therapy** has been tried in past years intermittently without striking success, compared to other methods. To date it does not appear to offer any substantial advantages over the "shock" therapies, and its results seem too unpredictable and insufficient to outweigh the hazards and difficulties of administration.

(c) **Frontal lobe neurosurgery.** Prefrontal lobotomy, leukotomy, and topectomy are, again, not strictly psychotherapeutic measures but are of interest here as surgical recourse for patients of otherwise poor prognosis who have failed to respond to other types of radical therapy. Remarkable results from such surgery have included the conversion of intractably agitated patients into placid individuals suitable to return home, and "deteriorated" backward psychotic patients into relatively self-sufficient cases requiring less custodial care. Unfortunately the results at this writing are widely variable and unpredictable. Since the results are irreversible and the mortality appreciable, frontal lobe surgery for the time being should continue to be restricted to those cases of near-hopeless psychotherapeutic prognosis.

(d) **Intensive personality analysis.** This includes psychoanalysis and Myerian "distributive" analysis, as well as many intermediate schools of therapy. For purposes of this discussion the first

two mentioned are most useful as representative psychotherapeutic disciplines, both of which require special training and organization of time which place them outside the practical reach of the non-psychiatrist. Classical psychoanalysis has been referred to earlier in this paper. Myerian "distributive" analysis stresses psychobiologic integration (the individual as a whole),[23] and distributes analysis selectively along lines of particular personality difficulty, as well as laying heavy emphasis upon socio-economic factors and the total life situation (Diethelm,[9] p. 111). Synthesis of personality assets accompanies the analytic procedures as data and insight accumulate, with the goal being a more purposeful psychobiologic adaptation to the total life situation (Billings,[5] pp. 234-239). Compared to classical psychoanalysis, it is evident that psychobiology presents a somewhat less inductive, more pragmatic methodology—having the disadvantages of less standardization, multiple variables, and probably being less objective as a scientific discipline; but having simultaneously the advantages of more flexibility, pragmatic expediency, and lending itself to specific application with the resultant saving in time for at least functional cures.

As mentioned, between these representative approaches to intensive psychotherapy lie many variations of technique and theoretical emphasis, including the experimental projects under way apparently leading to utilization of the contributions of both psychoanalysis and psychobiology.[3,21] As yet, the multiplicity of views and disagreements is testimony to the existence of an uncharted area between theory and practice of psychotherapy, making it more important to rely upon the selection of a man appropriate to the patient rather than to over-value the consultant's theoretical views. The differences are by no means as wide in the actual practice of psychotherapy as they appear to be in polemics on theory.

(e) **Hypnosis** is included in this section not because of any intrinsic difficulty or hazards in its practice with reasonably stable personalities, but rather because of the risk of precipitating occasionally a psychotic panic or involving the physician in a previously unrecognized delusional pattern. Because an unrecognized schizophrenic development may masquerade as a simple hysteria or anxiety reaction, the practice of hypnosis by non-psychiatrists is to be discouraged. As will be mentioned below, if a short-cut to analysis and synthesis is needed to circumvent conscious or pre-conscious resistance, it is this writer's opinion that narcosis interviews (with sodium pentothal or sodium amytal intravenously) are psychotherapeutically safer and more productive in the hands of the non-psychiatrist. Should a panic or psychotic reaction then be released during narcosis interview, one can at least control the emergency promptly (and probably render the patient essentially amnesic for the incident) by inducing full sleep.

2. **Conservative analytic techniques.** While these procedures are quite appropriate for the non-psychiatrist's use, provided he has the prerequisite interest and personality, they are used with more assurance when facilities are at least potentially available for psychiatric hospitalization in the event of an emergency.

(a) **"Non-directive"** interviews. As a term, this is probably a misnomer, since common-sense direction of a strictly limited sort is highly desirable. As discussed earlier in this paper, however the concept of passivity on the part of the therapist is one of the significant contributions of Freud to therapy, protecting the patient from standards and authority imposed arbitrarily by the doctor (which, if the patient accepts,

serve only to foster his dependency upon authority rather than to prepare him for independent solutions in the future). As Alexander[3] remarks, psychoanalytic treatment is a part of the patient's ego development—and not the doctor's "therapeutic act" upon the patient *via* interpretations. The same philosophy can be useful in non-directive psychotherapeutic interviews.

This approach requires, first of all, that the physician "listen out" the patient's story, although now and then mirroring back to the patient those statements which seem crucial or inconsistent—but scrupulously refraining from outright judgment or rebuttal. As discussion progresses, then, the physician may factually point out any obvious clues to emotional reactions associated with the subject at hand (tears, anger, flushing, hesitation, defensiveness, etc.), seeking to help the patient to accept openly his emotional attitudes as well as his stated problems. The therapist may summarize or (guardedly) interpret the patient's conclusions and attitudes—often in the form of a question—which serves to (1) demonstrate to the patient that his views are at least being recognized, (2) objectify the patient's assertions or denials by restatement, and (3) guide subtly the discussion by emphasis of selected material.

It may be protested that such passivity on the part of the physician is wasteful of his time and training—that the patient comes for help, not to talk until he stumbles upon his own answers. But this criticism, justified within limits, would also imply that the best teachers are those who solve the problems for their pupils. Corrective psychotherapy is, after all, a re-educational procedure—although as much concerned with the retraining of emotional patterns as of intellectual concepts. Socrates taught "non-directively;" *i.e.*, relied upon the assertions and conclusions of his pupils for material which, through reinterpretation and adroit questioning by him, led his students to accept new principles on their own terms. "A man convinced against his will is of the same opinion still." Corrective psychotherapy requires of a physician that he be more a teacher than an authority.

In contrast to the more superficial devices of persuasion, direction, and reassurance (discussed below), non-directive psychotherapy is indicated for personality conflicts of deeper origin, the solution of which is dependent upon insight acquired by the patient himself as he maintains reasonable initiative in the quest.

(b) **Narcosis** interviews (narco-diagnosis, narco-analysis, narco-synthesis). Interviews under narcosis with sodium pentothal or sodium amytal administered intravenously have become a valuable diagnostic and therapeutic weapon,[15] having been given great impetus during the war by Grinker and Spiegel.[13a] Analogous to hypnosis but safer from a psychotherapeutic standpoint in non-psychiatrists' hands, narcosis interviews provide a means of diminishing conscious and pre-conscious resistance (*e.g.*, fear, embarrassment, anxiety) to the release of underlying thoughts and feelings, allowing their aeration without loss of prestige by the patient. In addition to the subjective relief often experienced by the patient therefrom, the physician is provided with data for later discussion with the patient as well as for his own evaluation of the etiology and prognosis. In puzzling problems of differential diagnosis, the behavior, content, and mood of a patient while near-somnolent frequently supply pathognomonic evidence of the underlying psychopathology. Thus, for example, an agitated patient may react to narcosis with (1) striking relief of all symptoms, implying a relatively superficial dis-

turbance; or (2) sustained mood of despondency and futility, with self-depreciatory content implying a deep-seated depressive disorder (affective psychosis or severe reactive depression); or (3) expose delusional and hallucinatory material indicative of a potential or actual psychotic disorder of thinking. It is not meant to suggest that all reactions under narcosis are this clear-cut, but the technique is unquestionably becoming of great diagnostic and prognostic significance when combined with other clinical data.

The use, by Grinker and Spiegel,[13a] of narco-analysis in combat reactions emphasized the production of emotional catharsis by suggestively recreating the traumatic combat scene for the patient and encouraging him to re-enact the episode verbally and physically—this being followed by suggestive reassurance as the interview was terminated. Probably because of the multiplicity of stresses in civil life and the more gradual development of anxiety reactions, Grinker's abreactive technique is usually not suitable for civil practice. Verbal aeration (with emotional but not physical abreaction) of conflicts and tension is usually adequate when narco-analysis and narco-synthesis are effective.

The technique of administration is not difficult but is safest in a hospital setting where nursing observation, oxygen-carbon-dioxide, and stimulants are available when needed. Sodium pentothal is conveniently administered in a 5% intravenous solution in distilled water (0.5 gm. or gr. 7½ in 10 cc.) and given slowly (1 cc. per minute) until drowsiness and thickness of speech are attained, then is given more slowly to maintain the desired stupor throughout interview. Tolerance varies from 0.2 gm. (gr. 3) to about 0.6 gm. (gr. 9), but close observation is imperative because of the occasional hypersensitivity to the drug. I do not believe that more than 0.8 gm. is justified in a single interview, and if this amount is insufficient for narcosis the patient should be tried at a subsequent time on sodium amytal. Sodium amytal may be given in the same concentration as sodium pentothal but more slowly and injection terminated at a lighter stage because of sodium amytal's slower action and associated latent period before peak effect; after slight drowsiness and thickness of speech are observed, the needle may be withdrawn. The latent period ranges clinically from about 5 to 15 minutes, and the duration of adequate narcosis continues well beyond the length of the average interview. It is well to have parenteral stimulants (*e.g.*, "Desoxyn," picrotoxin, and/or epinephrine) available for use in event of too deep narcosis.

It is wise, also, for the physician to have assistance within call in the event that an uncontrolled agitation or psychotic reaction is precipitated; and, in the case of female patients, a nurse (in whom the patient has confidence) present in the room throughout narcosis. It is usually sufficient to assure the patient that he will experience a feeling of pleasant relaxation, in the course of which his tension will ease and he will find it easier to express his thoughts and feelings. If spontaneous aeration is insufficient or non-informing, production can then be guided by terse questions or suggestion, and the interview finally terminated with explanation and reassurance. Nursing attention serves to protect the patient from falling or otherwise injuring himself after interview is terminated and before somnolence has cleared (duration: 1 to 2 hours for sodium pentothal, 4 to 6 hours for sodium amytal). Mild doses of amphetamine derivatives are helpful in shortening the post-interview symptoms.

Narco-diagnosis usually requires only one interview; therapeutic narco-analy-

sis and narco-synthesis are more effective with at least 2, often 3 or more interviews, plus intervening discussions with the patient of content and affect released. Usually rapport is so much improved after one or more interviews that the patient can then voluntarily continue therapeutic interviews without (or with token doses of) a hypnotic. Certain patients are remarkably unproductive and tolerant of one or the other hypnotic agent; a trial of the alternative drug on subsequent interview often proves successful. A recent (and apparently unreported) modification of the technique seems very promising to increase productivity during interview; *viz.*, the simultaneous use of amphetamine derivatives (*e.g.*, "Desoxyn" 5-10 mgm. orally, ½ hour before administration of hypnotic).[7] While seemingly in opposition to the hypnotic, the stimulant results in much greater productivity during interview. Its use in narco-diagnosis, however, is probably confusing, since an underlying depression might be masked.

A useful evaluation of the present status of narco-diagnosis and narco-therapy has been contributed by Hoch.[15]

3. **Repressive-integrative techniques** (synthesis, support, persuasion, reassurance, direction). Procedures of this variety are so commonly used in all of medical practice that it would be pedantic to discuss them in detail. Obviously their appeal and efficacy are largely restricted to the patient's conscious awareness and controls, and they are primarily accepted upon faith in the authority of the physician. This is not to discredit their value but simply to emphasize that failures from their use can not reasonably be attributed either to (a) the physician's incapacity or misunderstanding, nor to (b) the patient's conscious unwillingness to accept advice. Failures will more likely occur because the approach is confined to a relatively superficial level of behavior and can have little influence upon the deeper, personality-determined motivations.

Since it is primarily the psychoneuroses and immaturity reactions the physician will be treating with "covering" techniques, it is important to have some working concept of their general etiology. Alexander's[3] definition fits this purpose: "Psychoneurosis is a failure of the individual to deal successfully with a given situation, a failure to find socially acceptable gratification for subjective needs under given circumstances. This failure depends upon the balance between the ego's adaptability and the difficulty of the confronting problem. When the situation demands greater powers of integration than the ego possesses, a neurosis develops. Whether the ego became incapacitated in childhood, adolescence, or adult life, and how it is limited by constitutional endowment, are secondary questions."

The "secondary questions," of course, from the point of view of this present discussion are exceedingly important practically in therapy, since superficial treatment can alter little the personality distortions arising in childhood or adolescence—unless effectively applied during those periods.

Certain aspects of repressive psychotherapy merit specific mention:

(a) **Reassurance, explanation.** The physician to whom the patient first goes with his specific symptomatology has a peculiarly powerful influence on the patient's subsequent attitude toward his illness. To be effective, reassurance can not be prematurely voiced, but must await reasonably adequate (but not obsessive) study—whether the symptomatology is predominantly organic or "functional." Reassurance can be nullified simultaneously by the physician's denial of

(1) obvious handicaps, (2) the validity of the patient's symptoms (though not organic in origin), or (3) the possibility of slow and intermittent resolution of symptoms.

One can not reassure the patient simply by denying the presence of disease. Fortunately the laity has a legitimate distrust of diagnosis by exclusion; thus one should not attempt to stop with the denial of an organic basis for symptoms. It is imperative to give the patient some reasonable explanation for his symptoms (beyond "Just Nerves"): specific situational stress, history of previous somatic reactions to emotional trauma, mechanisms of "functional" somatic symptoms, etc. Unless we do this, we fall into the fallacies of the "buck up and forget it" school of "psychotherapy"—and become major contributors to the business of charlatans by driving patients from ethical medical care.

The use of bibliotherapy (selected reading for patients) has been disappointing, and is not without considerable risk to an anxious and non-critical patient. Probably the most innocuous but still psychiatrically valid book suitable for almost any patient (and family) is a popular best-seller written by a layman (Rabbi Joshua Liebman's[19] *Peace of Mind*). This is a simply written description of certain emotional conflicts and the psychoanalytic philosophy of treatment, plus an attempt to reconcile psychiatric principles with religion. For patients in relatively stable adjustment and of good intelligence (and especially for parents and teachers having these qualifications, and who complain of "difficult" children) a more informative book by English and Pearson[11] (*The Emotional Problems of Living*) has been of considerable help in providing insight into personality growth and architecture. Over all, however, "bibliotherapy" is a misnomer—bibliographic references can be of prophylactic value to well individuals, but rarely are as therapeutic as they are disturbing to a psychiatrically ill patient.

Source-material for the physician, on the other hand, is relatively plentiful and of considerable value in providing him with a working knowledge of techniques, mental mechanisms, common misconceptions and pitfalls, etc., to aid in psychotherapeutic management. Although unfortunately widely scattered and presented in fragments, this information is well-formulated and available elsewhere[3,5,9,10,11a,13,14,17,18,20,21,25] and space does not permit a detailed review here.

(b) **Supportive measures.** Supportive care includes the use of such supplementary dietary and metabolic aids as are indicated by coexistent or related physical disturbances; plus reasonable attempts to restore more normal biologic rhythms (*e.g.*, reduction of insomnia, constipation). If the interference with biologic rhythms is severe, hospitalization for more sustained initial observation and control of medication is highly desirable. Tonic dosage of insulin ("regular" insulin, 10 to 30 units depending upon tolerance, ½ hour before meals) for hospitalized patients is often of value through relief of muscular tension, increased appetite and utilization of carbohydrates, and a subjective feeling of well-being. Other pharmacologic applications to supportive therapy are mentioned separately below.

(c) **Manipulation of environment and activity.** Medical recommendations for temporary or permanent alteration of the environment are of occasional help, especially when a patient needs (1) assistance in altering habitual patterns of behavior, (2) temporary respite or concessions from a stress-producing environment, and (3) introduction to new fields of endeavor. These are generally palliative devices, however, ranging

from hospitalization to protect a patient from well-meaning relatives to the urging of hobbies. Their use is not without its pitfalls; notably the fallacy inherent in "rest cures" which are based, as Karl Menninger[22] reasons, upon the fatigue theory of neurosis. Psychiatric illness, he points out, is the result of misdirected energy rather than the lack of energy. Groom[14] remarks that physicians should occasionally examine their own motives for sending anxious patients (far) away on vacations.

(d) **Pharmacologic aids.** The use of pharmacologic support in psychosomatic disorders is often fraught with more hazards than benefits, but if a conservative attitude prevails on the part of the physician and he is careful to imbue his patient with the philosophy that medications are intended to *reduce* symptoms temporarily rather than to *obliterate* them, it is hard to deny patients the reassurance of the excellent pharmacologic armamentarium now available. Some of the more useful drugs for this purpose may be grouped as follows: (1) rapid, delayed action, or slowly acting sedatives; (2) amphetamine sulfate and derivatives of rapid-acting type, for morning and noon stimulation of depressed and lethargic patients—preferably combined with minimal doses of a barbiturate to reduce tension and side-effects of amphetamine; (3) antispasmodics of recent development, relatively free of atropine side-reactions, for spastic gastrointestinal and other vegetative dyskinesias; (4) antihistaminics for severer allergic manifestations; and (5) bulk-formers for the conservative control of constipation.

A few safeguards seem particularly required in the pharmacologic treatment of psychiatric patients, since many of these individuals are potentially dependent upon any "crutch"—whether the crutch be mechanical, human, chemical, or institutional: (1) prescriptions for sedatives and stimulants should be non-renewable and for short periods (2 to 3 weeks); (2) sedatives, stimulants, and antispasmodics should be prescribed in almost homeopathic doses initially (except in emergencies), and the maintenance dose held at a very minimum; patients in the throes of anxiety frequently prove remarkably hypersensitive to even average doses; (3) alcohol, bromides, and narcotics have, in this writer's opinion, no place in psychotherapy except possibly when safer agents are not available for an emergency; (4) for older and arteriosclerotic patients, phenobarbital (or "Luminal") often produces unwarranted cerebral retardation and occasionally confusion; plain barbital, "Mebaral," sodium barbital, sodium amytal, paraldehyde, and the newer urea compounds are among the more desirable sedatives and hypnotics for these patients; (5) the use of hormonal substitution therapy (particularly gonadal) in cases of predominantly psychiatric symptomatology has been almost universally disappointing and scarcely justified (in the absence of gross organic indications) as an adjunct to psychotherapy; and (6) the availability of symptomatic remedies must not distract the physician nor his patient from the primary problem and the patient-as-a-whole, lest they be lost in a forest of symptoms with new distractions springing up as older ones are dampened pharmacologically or otherwise.

SUMMARY. Some of the present aspects of psychotherapy are surveyed for orientation of the non-psychiatrist:

1. Patients presenting mild to moderate psychopathology are often best treated by the non-psychiatrist, using proper criteria for selection and reasonable conservatism in the flexible use of psychotherapeutic techniques.

2. Successful psychiatric referral is heavily dependent upon the rational selection both of the patient as suitable and the psychiatrist as appropriate to the patient and his problem.

3. The referring physician plays a powerful role in determining the patient's attitude toward his symptomatology, as well as toward subsequent psychotherapy. Some preparation of the patient for the latter before referral (*i.e.*, indications, rationale, practical problems related) can greatly facilitate successful psychiatric management.

4. Present trends in psychotherapeutic practice give promise of more pragmatic adaptation of previously divergent theories.

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PROCEEDINGS OF
THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA
SESSION OF FEBRUARY 17, 1948

The Renal Elimination of Caronamide (4′-carboxyphenylmethanesulfonanilide). HAROLD M. PECK, M.D., ELIZABETH K. TILLSON, WILLIAM S. WALLER and KARL H. BEYER, Ph.D., M.D. (Medical Research Division, Sharp and Dohme, Inc., Glenolden, Penna.). Caronamide (4′-carboxyphenylmethanesulfonanilide) has been demonstrated to be an effective agent for the inhibition of the renal tubular excretion of penicillin. The hypothesis for such an agent provided that it reversibly inhibit the tubular excretion of penicillin by an affinity for the tubular transport mechanism involved and that it be eliminated essentially by glomerular filtration.

Experimental procedures for the study of renal elimination of caronamide in dogs have included the following: 1) Simultaneous plasma concentrations of caronamide and mannitol, over an 8-hour period, in bilaterally nephrectomized, unanesthetized dogs. 2) Simultaneous urinary recoveries of caronamide and mannitol. 3) Simultaneous falling plasma concentrations of caronamide and mannitol. 4) Clearance ratios, excretion ratios, and extraction ratios of caronamide obtained by comparing its clearances and extractions to those of creatinine.

Analytical methods included the colorimetric method of Ziegler and Sprague (J. Lab. Clin. Med., **33**, 96, 1948) which measures caronamide per se and its metabolites and the method of Brodie, Levy and Bernstein (J. Pharm. and Exper. Therap., **91**, 246, 1947) which measures caronamide per se. Correction for binding on plasma protein was based on results obtained by the method of Lovietts (J. B. C., **120**, 267, 1937).

The results obtained justified the following conclusions: 1) Caronamide undergoes some alteration in the body that increases its water solubility but does not seem to alter the manner in which the kidney handles the drug. 2) Practically all of a dose of caronamide administered orally or intravenously is recovered as such, or in the form of metabolites, in the urine. 3) Present evidence indicates that caronamide and its metabolites are excreted by glomerular filtration. 4) The clearance of caronamide is inversely related to its plasma concentration. 5) Present evidence permits the tentative conclusion that bound, as well as unbound, caronamide contributes to the amount filtered, rendering a correction for binding an uncertain quantity of questionable significance.

Comparison of Two Types of Permanent External Bile-fistula Dogs for Studying Liver function. WILLIAM J. SNAPE, M.D., C. WILMER WIRTS, M.D., and ABRAHAM CANTAROW, M. D. (Depts. of Physiology, Medicine, and Biochemistry, Jefferson Medical College.) A tubulated duodenal fistula, of the type first described by Thomas, placed opposite the biliary ampulla was utilized to collect bile. This type of bile-fistula is compared with the Rous-McMaster fistula preparation. Some of the advantages of the Thomas-fistula dog are (a) it has a shorter period of convalescence, (b) requires no special diet or care, (c) survives for long pe-

riods of time, (d) maintains good liver function and freedom from extra hepatic obstruction. Comparing the two preparations it was found that all of the Thomas-fistula dogs met the criteria for normal bromsulfalein excretion in the bile, while only six out of twenty-two of the older type (Rous-McMaster) met these requirements. None of the newer type preparations showed any bromsulfalein retention while four of the five standard animals exhibited this abnormality. The volume of bile excreted per unit of time was almost identical in the two preparations. However, in general the older type fistula dog did not excrete as much dye as the Thomas-fistula dog. Therefore, it would seem that rather than an obstruction to the flow of bile actually these animals had liver impairment.

Comparing the 2 mgm./kilo dose and the 5 mgm./kilo dose of bromsulfalein we find the concentration in the bile to be enormously increased but the shape of the excretion curve and the concentration at the end of two hours are practically identical.

The preparation described has been found useful in comparing rates of excretion of various injected materials and evaluation of various choleretics.

Variations in the Blood-supply of the Liver, Gall Bladder, Stomach, Duodenum, Pancreas and Spleen (200 dissections).* NICHOLAS A. MICHELS, Dr. Sc. (Daniel Baugh Institute of Anatomy, Jefferson Medical College). In my previous work (Am. J. Anat., 1942) it was shown that in 100 bodies each spleen had a different terminal divisional pattern of the splenic artery. Total splenic arterial bed length varied from 30-90 cms., length of splenic from 8-32 cms. marked tortuosity), lienal branches from 7-35, some arising early (distributed splenic), others late (magistral splenic).

Like the spleen, each liver has a different pattern of terminal arterial vascularization. In 52% the celiacal hepatic supplies a right, left and middle hepatic, the latter a branch of right or left hepatic supplying quadrate lobe. The 3 main hepatic branches give off numerous terminal branches (20-65) each selectively distributed to a specific liver area as is readily observed when branches in the umbilical fossa are dissected.

An aberrant hepatic artery (one arising otherwise than from celiacal hepatic) occurs nearly in every other body (48%). Aberrant right hepatics arise prevailingly from superior mesenteric; aberrant left hepatics from left gastric. Of aberrant right hepatics (22%), 15.5% were replaced right hepatics, i.e., the only right hepatic present; 6.5% were accessory right hepatics. Of aberrant left hepatics (26%), 14% were replaced left hepatics, 12% were accessory left hepatics. Predictable estimate: Nearly every other aberrant left hepatic from left gastric constitutes the only left hepatic present and 3 of every 4 aberrant right hepatics from superior mesenteric are replaced right hepatics. Entire hepatic trunk may come from superior mesenteric or left gastric.

Single cystic artery from right hepatic 58.5%; replaced types 16.5%. Double cystic 24.5%; one triple. Right hepatic ventral to hepatic duct, 14.5%. Accessory hepatic ducts, 14%.

Investigation showed constancy of four arteries usually not described in text-books: 1) retroduodenal (first br. of gastroduodenal) to back of duodenum and head of pancreas; 2) supraduodenal to first part of duodenum; 3) dorsal pancreatic (from splenic, hepatic, celiac, sup. mesenteric); 4) trans-

* Aided by a grant from the American Philosophical Society.

verse pancreatic, which courses along inferior surface of pancreas.

Direct Experiments on the Interpretation of the Ballistocardiogram. O. HORWITZ, M.D., R. L. MAYOCK, M.D., and ISAAC STARR, M.D. (Depts. of Therapeutic Research and Medicine, Univ. of Penna.) At the first stage of necropsy the aorta has been cannulated at the aortic valve. The cannula, bent at a 90° angle, was attached to a piston syringe. A Hamilton manometer was inserted in the aorta, and "diastolic" pressure maintained by saline solution running into the femoral artery from a bottle raised to the diastolic level. The subject lay on the ballistocardiograph and the position of the syringe plunger, and the blood pressure were recorded simultaneously with the ballistocardiogram by appropriate optical systems. "Systoles" of various types were obtained by pushing home the plunger by hand, or by striking it with a padded mallet. The records of 29 such systoles, obtained on two cadavers with normal blood vessels, aged 22 and 14 years, have been analysed.

The *shape* of the ballistocardiogram depends on the shape of the ejection velocity curve; when the latter attains maximum velocity early in systole the ballistocardiogram is normal in form. Otherwise it is abnormal.

The *size* of the ballistocardiogram depends on the acceleration of the ejected fluid. The correlation between maximum positive acceleration and the area of I and J waves is +0.72, between maximum positive acceleration and the area of I + J divided by their duration is +0.84. The amplitude of the ballistocardiogram is, therefore, primarily related to the heart's force, and as the duration is known, to the heart's power. The relation to cardiac output is secondary.

Nevertheless the calculated values for cardiac output, adjusted for the lack of right sided effects by doubling the I wave area, agree fairly well with the actual. In only 8 instances was the ballistocardiogram normal in form and the pulse rate, calculated from the duration of ejection, between 43 and 200. In these, the average difference between actual and calculated stroke volumes was +1%, the standard deviation about this mean 13%.

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BOOK REVIEWS AND NOTICES

TEACHING PSYCHOTHERAPEUTIC MEDICINE. Edited by HELEN LELAND WITMER, Ph.D. Pp. 464. New York: The Commonwealth Fund, 1947. Price, $3.75.

THIS "Minnesota Experiment" has important meaning for every practitioner of medicine. Twenty-three physicians in general practice, a pediatrician and a dermatologist met 7 psychiatrists and 2 internists in an outpatient clinic where they worked and talked for 2 weeks—from 8:30 A. M. to 9 P. M.

Talks by psychiatrists on such topics as Normal Personality Development, Anxiety, Emotions and Disease were followed by informal section meetings and, most important, hour-long interviews between the physicians and out-patients. Sometimes a psychiatrist would come into the last minutes of an interview. In the second week some explanations of the psychoneuroses were given and illustrated by clinical examples and physiological demonstrations of the effects of emotion on body functions.

Appraisals of the value of this experiment are deservedly enthusiastic. Physicians to whom patients turn first in every kind of illness learned to deal with easily understandable methods of psychotherapy which were superficial but which could bring surprisingly good results. They learned also to recognize malignant mental conditions which were either to be let alone or referred to psychiatrists.

An invaluable contribution was made by internists Drs. Bauer and Wolff in fitting organic disease and the play of emotion into the life situations of patients.

This book is strongly recommended to all physicians. The Commonwealth Fund has scored a great success in this experiment.

E. B.

HANDBOOK ON FRACTURES. By DUNCAN EVE, Jr., M.D., F.A.C.S., Assoc. Prof. of Surgery, Vanderbilt Univ. Pp. 263; 129 ills. St. Louis: C. V. Mosby, 1947. Price, $5.00.

THIS concise, little book on fractures is remarkably replete with the essential principles and is illustrated with very informative photographs and line drawings. It should be an excellent aid as a handbook in the teaching of fractures, representing a summation of more than 40 years in the field of fracture work by a busy and practical surgeon. Dr. Eve is to be congratulated.

P. C.

THE PATHOLOGY OF NUTRITIONAL DISEASE. By RICHARD H. FOLLIS, Jr., M.D., Assoc. Prof. of Pathology, Duke Univ. School of Medicine. Pp. 291; 71 ills. Springfield, Ill.: Charles C. Thomas, 1947. Price, $6.75.

THE subject of nutritional disease has become so vast that it tends to be bewildering to one not closely connected with the field. Nevertheless, Dr. Follis has managed to condense the subject into a concise, readable volume. The pathologic changes in both experimental animals and in man are clearly described and well illustrated by copious photographs. Topics discussed include the essential elements, essential amino acids, and vitamins. For each substance, a brief historical review and discussion of biochemical relationships is given in addition to a description of pathologic changes. This volume should prove of value to both pathologist and clinician.

A. R.

APPLIED MEDICAL BACTERIOLOGY. By MAX S. MARSHALL, Ph.D., with the collaboration of HANET B. GUNNISON, M.A., ALFRED S. LAZARUS, Ph.D., ALIZABETH C. MORRISON, M.A., and MARIAN C. SHEVKY, A.B., Medical Center of the Univ. of California. Pp. 340; 8 ills. Phila.: Lea & Febiger, 1947. Price, $4.50.

THIS book is a new approach to medical bacteriology. Although it is not a text in the usual sense, principles of bacteriology and procedures for the identification of microorganisms are skillfully combined as a laboratory manual. Thus the first 14 chapters are concerned with general bacteriologic procedures including such valuable chapters as those on general virus techniques, sanitation and biologic products. The final chapter constituting about half the book is devoted entirely to the laboratory diagnosis of commonly encountered infectious lesions or diseases. These are arranged alphabetically in order to facilitate reference. Under each disease are discussed the clinical aspects, the procurement of specimens, the character and identification of the causative organisms, and suitable methods of reporting laboratory findings to the clinical services. This book should be useful therefore not only for bacteriologists and pathologists, but also for practitioners of medicine in the proper procurement of specimens for bacteriologic examination.

R. N.

PROTEINS AND AMINO ACIDS IN NUTRITION. Edited by MELVILLE SAHYUN, M.A., Ph.D., Biochemist Consultant, Charles Godwin Jennings Hospital, Detroit. Pp. 566. New York: Reinhold, 1948. Price, $7.50.

IN THIS cooperative effort, 18 authors have joined to prepare 13 chapters ranging from a historical review of the early literature upon protein nutrition to the protein nature of filtrable viruses. As the title implies, the authors confine themselves to various facets of our knowledge of proteins in nutrition. A partial listing of chapters will indicate the variety of information covered: "The Biological Utilization of Proteins and Protein Requirements"; "Caloric, Vitamin and Mineral Requirements with Particular Reference to Protein Nutrition"; "The Nutritive Aspects of Meat and Meat Products"; "The Relation of Hormones to Protein Metabolism"; "Plasma Proteins and Their Relation to Nutrition"; "Protein and Amino Acid Nutrition in Pediatrics and in Pregnancy"; "Protein Nutrition in Surgical Patients"; "Proteins as Related to Burns"; "Relation of Fluid and Mineral Balance to Protein Metabolism"; "The Protein Nature of Toxins, Antitoxins and Related Substances". In the appendix are included 2 tabulations of the proximate composition of American food materials and the nutritive values of 100 grams of selected foods, edible portions.

With this varied content it is evident that the biological significance of proteins and amino acids is being actively investigated. The answers to many of the questions raised are not yet available, but the discussions presented here should stimulate further investigations and increase our knowledge.

H. V.

CONGENITAL MALFORMATIONS OF THE HEART. By HELEN B. TAUSSIG, M.D., Assoc. Prof. of Pediatrics, Johns Hopkins Univ. School of Medicine. Pp. 618; 223 ills., 46 in color. New York: The Commonwealth Fund, 1947. Price, $10.00.

THIS book is divided into 4 parts. The first (Chapters I through III), serving as an introduction deals with embryology, physiology and diagnostic methods. In Parts II and III (Chapters IV through XXV) the various congenital heart malformations are discussed. Finally, therapy is presented in Part IV (Chapters XXVI and XXVII).

Each chapter has been given the same care in organization and presentation as that reflected by the over-all plan of the book. Clinical and pathological findings are amply illustrated with drawings of pathological specimens, with good reproductions of representative X-ray films, and in a few selected cases, with limb lead electrocardiograms. The anatomical alterations in the circulation produced by the various malformations are well shown by colored plates. Each chapter is concluded with a summary, a few illustrative cases, and several pertinent references to the literature.

In preparing this book Dr. Taussig has relied almost entirely upon her own experience to provide material. Many of the clinical observations and interpretations are her own, especially those based on fluoroscopic studies. She has made no attempt to survey the literature dealing with congenital heart disease or to list a complete bibliography.

Throughout the book Dr. Taussig emphasizes the importance of the clinical methods available to all physicians in the diagnosis of congenital heart malformations. This emphasis is justifiable as is the stress placed upon embryology, pathology, and physiology. There is, however, no specific discussion of the relative incidence of the various malformations, and much valuable information obtainable by angiocardiography and catheterization of the heart has been omitted. Passing mention is made of the diagnostic value of these procedures in certain malformations. Likewise no use has been made by the author of chest leads in the electrocardiographic studies.

This book is much needed and should prove useful to all physicians interested in congenital heart disease. It can be recommended without hesitation.

R. K.

GYNECOLOGIC AND OBSTETRICAL UROLOGY. By HOUSTON S. EVERETT, M.D., Assoc. Prof. of Gynecology, The Johns Hopkins Univ. 2d ed. Pp. 539; 232 ills. Balt.: Williams & Wilkins, 1947. Price, $6.00.

WITH its emphasis on the very important relationship between diseases of the female genital system and the urinary tract, this book is a most valuable contribution, filling the gap commonly found in the literature and textbooks of these 2 specialties.

The field of urology, excluding only that which strictly pertains to the male, is completely covered by the author. The sections on anatomy, physiology and on renal function studies are excellently written, up to date, and beautifully illustrated, using many of the classic drawings of Max Brödel, as reproduced out of earlier texts originating from

the Johns Hopkins group. Diseases of the Female Urethra, Inflammations of the Bladder, Incontinence of Urine, Ureteral Obstructions, Pyelonephritis, Urinary Fistulas and The Management of Surgical Injuries to the Urinary Tract are ably presented, emphasizing etiology, diagnosis and management of these difficult problems in the female and bringing to the reader the summation of the work of many observers from a large clinic limited to urology in the female.

The new edition includes a section on the technique of indirect cystoscopy; a revision of the chapter on bladder neoplasms so as to include a summary of Jewett's recent work; the newer concepts of chemotherapy; and an increased number of illustrations and tables.

J. G.

TELEPATHY AND MEDICAL PSYCHOLOGY. By JAN EHRENWALD, M.D., Associate in Psychiatry, Long Island College of Medicine. Pp. 212. New York: W. W. Norton, 1948. Price, $3.00.

THE possibility of telepathic communication between individuals has frequently challenged the imaginative powers of the pseudo-scientific and lay writers, but the evidence presented has been mystic or poetic rather than objective and subject to critical scrutiny. Observations of the extreme sensitiveness of neurotic and psychotic patients to the attitudes of those around them do not readily lend themselves to re-examination under laboratory conditions; and on the other hand, the work of Dr. J. B. Rhine of Duke University with the so-called Zener cards provides data which are statistically assayable but provides little information as to the modus operandi of the phenomenon.

On this gap Dr. Ehrenwald focuses his interest. His association with "the Viennese school of Psychiatry" gave him, he feels, a psychoanalytic orientation and a lack of bias toward the schools of Freud, Adler, Jung and Stekel. Certainly he makes every effort to present an unprejudiced point of view. He contends that telepathic activity plays a more important rôle in the psychoanalytic situation than most therapists are willing to grant; and he adds the piquant comment that "no orthodox psychoanalyst appears to have ever come across patients dreaming in the 'Adlerian' jargon and . . . no strictly 'Adlerian' analyst has observed patients using the dream codex of the orthodox psychoanalyst . . . ." In spite of the serious considerations of telepathic phenomena in present-day psychoanalytic literature, there would appear to be some justification for the author's statement that these are regarded as "merely accidental" occurrences rather than as therapeutic tools of some potential value.

When considered from this point of view telepathy, in the author's opinion, may be expected to play a significant part in the formation of personality and the changes observed in the neuroses and psychoses. The concept is thought-provoking and the case-material (except, perhaps, in the chapter on Telepathy and Paranoia) offers strong supportive evidence. Whatever the reader's point of view, Dr. Ehrenwald's book is timely and stimulating.

E. B.

THE SULFONAMIDES AND ALLIED COMPOUNDS. By ELMORE H. NORTHEY, Ph.D., Administrative Director, Stamford Research Laboratories, American Chemical Monograph Series. Pp. 660; 323 tables. New York: Reinhold, 1948. Price, $12.50.

SINCE the discovery of the antibacterial activity of the sulfonamides and related compounds, over 5000 new compounds have been synthesized. Much duplication of effort has gone into the preparation of these substances. Pertinent data upon their chemical and pharmacological properties are so scattered in the literature that it is all but impossible for the individual worker to attempt to correlate them. Accordingly Doctor Northey has compiled the information upon these compounds into tables in Beilstein order, listing melting points, antibacterial activities when known, and references to the literature. Many unpublished data are included, and journal references through December, 1944, are listed.

These data should be of great value as a research tool in the quest for new chemotherapeutic drugs. The book is not intended for a therapeutic guide, though it does contain much of interest to pharmacologists and clinicians. The methods of experimental evaluation of chemotherapeutic activity are summarized together with a tabulation of published data on the action of sulfa drugs against particular bacteria. The pharmacology of the more important compounds is presented in a separate chapter. The various theories advanced to explain the mechanism of action of the sulfonamide drugs are also reviewed. In a final chapter Doctor B. W. Carey presents an adequate summary of the clinical evaluation of the sulfonamide drugs.

H. V.

NEW BOOKS

Medical Clinics of North America. January, 1948. Chicago Number. "Symposium on Endocrinology." Pp. 1-299. Phila.: W. B. Saunders. Price, $16.00 a year.

THIS number is composed of 11 articles under the Editorship of Dr. Willard O. Thompson, and, in addition, 11 Clinics on other subjects. The Symposium on Endocrinology discusses in practical detail such problems as sterility in the male and female, hypogonadism in the male, uterine bleeding, testosterone treatment of breast cancer, problems of growth and the treatment of Graves' disease with radioactive iodine. The articles, by authors who are recognized authorities in their fields, present a thoughtful analysis of the problems involved. The Clinics on other subjects are diverse, ranging from an excellent discussion of the detection of food allergy to a review of precordial leads in electrocardiography. The volume may be recommended for these practical yet stimulating articles.

F. D.

NEW EDITIONS

Illustrative Electrocardiography. By JULIUS BURSTEIN, A.B., M.D., Chief of the Cardiac Clinic, Morrisania City Hospital, New York, and NATHAN BLOOM, M. D., F.A.C.P., Assoc. Prof. of Medicine, Medical College of Virginia. 3rd ed. Pp. 325; 99 plates. New York: D. Appleton-Century, 1948. Price, $6.00.

THIS edition is rewritten and includes, very briefly, the newer techniques of electrocardiographic examination. The text contains few theoretical considerations, and no controversial material. The illustrations are well chosen. Chapters on the phonocardiogram and radiology of the heart have been added. There is no bibliography, but a subject index is appended. The book is distinctly one for the beginner, and, as such, will serve a useful purpose.

J. V.

Laboratory Technique in Biology and Medicine. By E. V. COWDRY, Prof. of Anatomy, Washington Univ. 2d ed. Pp. 269. Balt.: Williams & Wilkins, 1948. Price, $4.00.

EXCEPT for a few introductory pages on Choice of Method and Standardization of Stains, the text consists of techniques (histological, physiological, biophysical and biochemical) conveniently arranged in alphabetical order. This edition "has expanded the subject matter to include related physical methods, and microchemical and other laboratory techniques. . . . Also included are new methods developed since the publication of the first edition, and improvements in standard techniques."

Laboratory Experiments in Physiology. By W. D. ZOETHOUT, Ph.D., Prof. Emeritus of Physiology, Chicago College of Dental Surgery. 4th ed. Pp. 263; 97 figs. St. Louis: C. V. Mosby, 1948. Price, $3.00.

"THE book is designed to serve as a useful guide for courses ranging from elementary human physiology to advanced mammaliam or medical physiology."

Source Book of Orthopaedics. By EDGAR M. BICK, M.D., F.A.C.S., Assoc. Orthopedic Surgeon, Mt. Sinai Hospital, New York. 2d ed. Pp. 540; 31 ills. Balt.: Williams & Wilkins, 1948. Price, $8.00.

Psychobiology and Psychiatry. By WENDELL MUNCIE, M.D., Assoc. Prof. of Psychiatry, Johns Hopkins Univ. 2d ed. Pp. 620; 70 ills. St. Louis: C. V. Mosby, 1948. Price, $9.00.

Clinical Toxicology. By CLINTON H. THIENES, M.D., Ph. D., Prof. of Pharmacology, Univ. of Southern California, and THOMAS J. HALEY, Ph. D. 2d ed. Pp. 373; illustrated. Phila.: Lea & Febiger, 1948. Price, $4.75.

SINCE the 1st edition appeared 8 years ago (See AM. J. MED. SCI., *199*, 726, 1940) the text has been so greatly enlarged and revised that the book has been completely reset. It is divided into 9 sections, Convulsant Poisons, Central Nervous System Depressants, Peripherally Acting Nerve Poisons, Muscle Poisons, Protoplasmic Poisons, Poisons of the Blood and Hematopoietic Organs, Principles of Treatment, An Outline of Symptom Diagnosis, Chemical Diagnosis of Poisoning. It should be of value to the general practitioner and to specialists in many fields.

Thromboendangiitis obliterans des Gehirns. Von Dr. med. F. LLAVERO. Pp. 248; 15 ills. Basle, Switzerland: Benno Schwabe, 1948. (Imported by Grune & Stratton.) Price, Geb. Fr. 24.

Uber die Kaliumbestimmung in Biologischer Substanz. VON W. W. RIEBEN, Professor der Medizin. Pp. 73; 4 ills. Basle, Switzerland: Benno Schwabe, 1947. (Imported by Grune & Stratton.) Price, Geb. Fr. 12.

You Can Be Thin! Slenderness Through Psychology. By HERMAN FRIEDEL, M.D. Pp. 117. New York: Caxton House, 1948. Price, $2.00.